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Chemoselective flow hydrogenation approaches to isoindole-7-carboxylic acids and 7-oxa-bicyclio [2.2.1]heptanes†

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Two libraries of highly decorated norcantharidin analogues were accessed *via* a series of sequential chemoselective flow hydrogenations and solvent-free transformations. Utilising a 10% Pd/C catalyst, modifications to reaction parameters (H_2 pressure, temperature and flow rate conditions) allowed facile access to effect selective direct reductive aminations and olefin reductions in the presence of furan, benzyl and nitrile moieties were established. The use of 20% $Pd(OH)_2$/C; Pd tetrakis; 5% Pt/C (sulfided) gave mixtures of furan and olefin (both reduced) and olefin reduced products. RuO_2; 0.5% Re/C and Re_2O_7 resulted in no reduction. Concurrent olefin and nitrile reduction was achieved in the presence of furan moieties by employing a RANEY® nickel catalyst. In total, 31 reaction conditions were examined using less than 200 mg of reagents allowing optimised conditions to be efficiently determined. These optimised hydrogenation conditions afforded desired analogues in near quantitative yields thus removing the requirements of reaction workup and chromatography.

Introduction

Adult members of the Meloidae family of Coleoptera (beetles) deter attacks from many predators by discharging droplets of cantharidin-laden blood reflexively from their hind leg joints.[1] These cantharidin (**1**) rich secretions are also used as a copulatory gift to protect the fertilised eggs from predation.[2,3]

Cantharidin, in the form of the dried body of the *Mylabris* beetle, has a long history of use in Chinese traditional medicine for treatment of dermal conditions and tumours with the first chemotherapeutic application reported in 1264.[3] Cantharidin and norcantharidin are potent inhibitors of the serine/threonine protein phosphatases, especially protein phosphatases 1 and 2A.[4,5] The interplay between protein kinases, which add phosphate to mainly serine and threonine residues, and phosphatases, which remove phosphate moieties, modulates the vast majority of cellular signal transduction events including neurotransmission, muscle contraction, glycogen synthesis, T-cell activation, and cell proliferation.[4,6] Cantharidin is nephrotoxic, and this has prevented its widespread use in Western medicine where current use is limited to topical applications.[7,8] However, the demethylated norcantharidin (**2**) has no such nephrotoxicity issues and has thus been the subject of a considerable number of anti-tumour studies (Fig. 1).[9–17]

We and others have exploited the 7-oxa-bicyclo[2.2.11] heptane scaffold in drug development programs geared towards developing tumor suppressing agents.[9–17] We have also demonstrated that the scaffold exhibits promising levels of activity against *Plasmodium falciparum*,[18] and *Haemonchus contortus*.[19] Fig. 2 shows representative examples of analogues investigated in these studies, and include the benzoyloxymethyl-substituted norcantharidins (**3** & **4**),[20] the acid amides (**5**),[21–23] anhydride modified ethers (**6**),[24,25] norcantharimides (**7** & **8**),[36,37] the bis-norcantharimides (**9** & **10**),[23,26] the tetracyclic norcantharimides (**11** & **12**),[12] along with the tetracyclic-bisnorcantharimides (**13** & **14**).[26]

In addition to our medicinal chemistry interest we have a keen interest in the application of green chemistry approaches to the development of focused compound libraries. This, coupled with our prior report of the pivotal nature of the 7-oxa-bicyclo[2.2.1]heptane moiety,[27,28] prompted us to examine potential expedient and green approaches to analogues such as **20** and **24** (Fig. 3). We envisaged that analogue series' based on **20** (isoindole-7-carboxylic acids) and **24** (7-oxabicyclo[2.2.1]-heptane carboxylic acids) could be expediently accessed

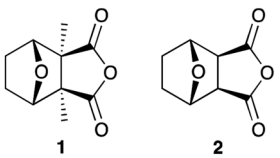

Fig. 1 Chemical structures of cantharidin (**1**) and the demethylated analogue norcantharidin (**2**).

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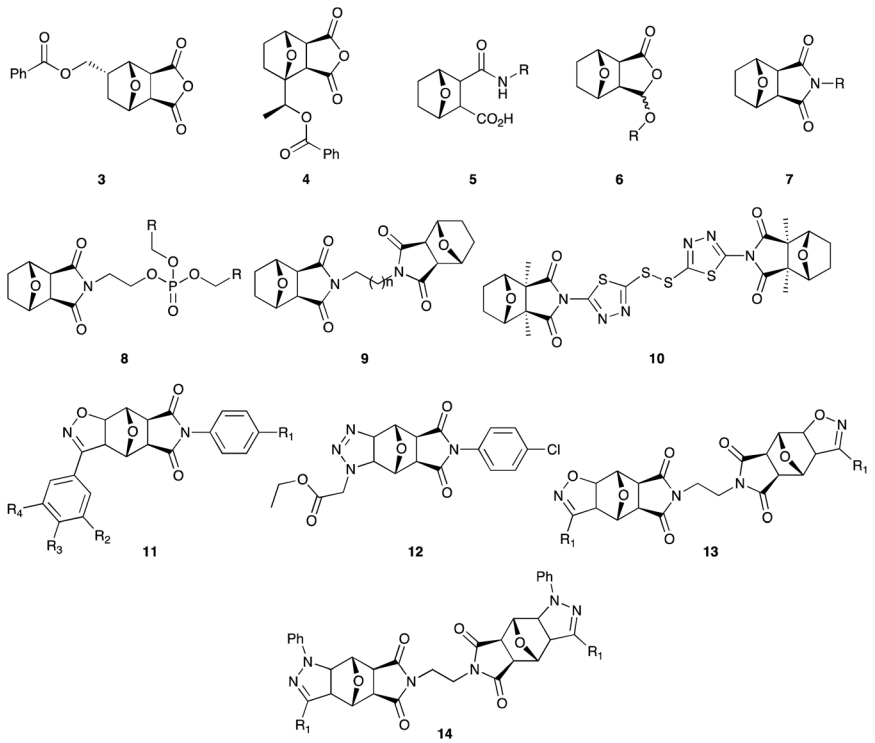


Fig. 2 Illustrative examples of previously reported 7-oxa-bicyclo[2.2.1]heptane analogues.[12,14,21,37]

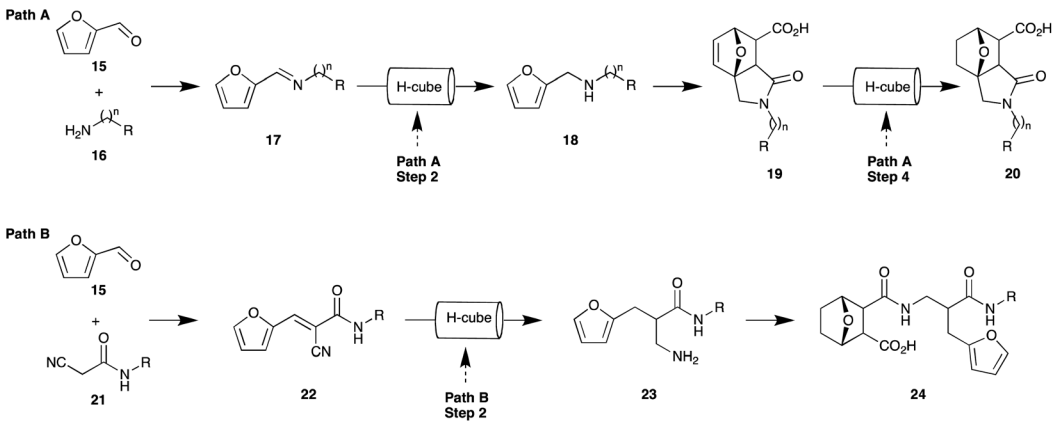


Fig. 3 Proposed sequential flow pathways **Path A** and **Path B** to provide access to analogues of compound **20** and **24**, respectively. (R-groups defined for **Path A** and **Path B** in Table 1 and Fig. 4, respectively).

through the development of sequential flow pathways *i.e.* **Path A** and **Path B**, respectively. **Path A**, which is adapted from a number of previously reported protocols, would allow interrogation of the scaffold adjacent the 7-oxo-bridge head,[29–32] a region which is poorly described in the literature,[33] whereas **Path B** would provide a means of incorporating analogues of cyanoamide **22**, which displays cytotoxicity against a range of carcinoma cells,[34–36] into the norcantharidin scaffold.

Common to both pathways is a series of reductive approaches including reductive amination (**Path A**, Step 2), olefin (**Path A**, Step 4 & **Path B**, Step 2), and nitrile reductions (**Path B**, Step 2). We envisaged that each of these reductions could be effected and rapidly optimised using minimum reagents quantities by careful manipulation of the flow hydrogenation conditions, *i.e.* judicious choice of catalysts, H_2 pressure, temperature, and flow rate. However at the outset, we were also cognisant that furan reduction and de-benzylation were potential undesirable outcomes. Protocols to reduce furan analogues using platinum group metals have been well documented,[38,39] and recently a number of highly diasteroselective protocols to access optically active tetrahydrofurans from furans have been reported[40–43] in addition to asymmetric hydrogenation of thiophenes and benzothiophenes.[41,44,45] These protocols use a range of platinum based catalysts, high pressures, typically in the range of 30–90 bar H_2 pressure, temperatures up to 80 °C and long reaction times. We anticipated that,

by screening milder reduction conditions and exploiting the exquisite control of temperature, pressure, and catalyst exposure provided by the ThalesNano H-cube™ (H-Cube), reaction conditions could be tuned to afford the desired selective reductions. Additionally the reduced contact (residence) times afforded by flow chemistry potentially allowed for the isolation of partially reduced intermediates unlike the corresponding batch chemistry approaches. While flow chemistry can be considered inherently green as a consequence of low material usage during process optimisation, we also sought to use easy to recycle solvents[46,47] and processes that facilitated ease of product access and purification.[48,49]

Results and discussion

Our investigation commenced with a model coupling of furan-2-carbaldehyde (**15**) with 4-methoxybenzylamine (**16a**) Step 1 of **Path A** (Fig. 3 and Scheme 1), using our previously reported direct reductive amination protocol.[50] Briefly, 0.05 M methanolic solution of furan-2-carbaldehyde (**15**) and 4-methoxybenzylamine (**16a**) were passed through the H-Cube equipped with a 30 mm 10% Pd/C catcart™, under 50 bar H_2 at 50 °C, with a flow rate of 1 mL min^{-1}. Each optimisation step was conducted for 10 min allowing collection of a 10 mL sample for ^1H NMR and GC-MS analysis. Analysis indicated quantitative conversion to the desired adduct **18a** (imine **17a** was not isolated) with no evidence of furan reduction or de-benzylation evident.

With **18a** in hand, our attention turned to the sequential Diels–Alder and lactam formation (Step 2, **Path A**, Scheme 2). This two-step transformation proceeded smoothly and in excellent overall yield (69%) with the product collected by filtration after trituration with diethyl ether. The diethyl ether was recovered and reused in the trituration of the hydrogenated product (below). Access to compounds such as **19a–h** allow, on treatment with protic ionic liquids, entry to N-substituted 5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamides and N-substituted 3-oxisoindoline-4-carboxylic acids. This current approach allows greener access to these 7-oxoisoindole analogues.[29]

The final step of reaction **Path A**, olefin reduction, was again carried out using the H-Cube charged with a 30 mm 10% Pd/C catcart™ (50 bar H_2, 50 °C, and a flow rate of 1 mL min^{-1}). Trituration of the eluent with diethyl ether afforded the desired analogue **20a** in >95% purity (Scheme 2).

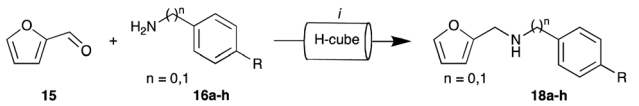
With our model system, the sequential flow reaction protocol of **Path A** afforded the desired bicyclo[2.2.1]heptane analogue **20a** in excellent overall yield (51%, 3 steps) with no chromatography requirement. More broadly the two 10 min flow chemistry steps and one batch reaction allowed rapid access to a diverse library of analogues with a range for functional groups (Table 1, **20a–g**) and anilines tolerated (Table 1, **20h**) and afford 25–50 mg (sufficient for all preliminary biological screening) of the desired products in >95% purity by trituration. This protocol offers dramatic reductions in reaction times and eliminating the requirement for catalyst preparation, reaction work-up, and chromatography typically used to access compounds of this nature.[22,29] In keeping with previous reports on the use of Pd-based catcarts™ we detected no Pd-leakage or residue in the products isolated.[51]

Having successfully developed a small library of analogues using **Path A**, our attention turned to the second proposed sequential flow pathway, **Path B** (Fig. 3). Access to the desired furan acrylamides (**22a–22c**) was *via* a solvent free condensation of methyl cyanoacetate and small library of benzylamines. The initial synthesis examined the use of 4-methoxybenzylamine (**16a**) to afford cyanoamide **21a** which was used directly in the Knoevenagel condensation with furan-2-carbaldehyde (**15**) at room temperature giving **22a** in a 71% yield (2 steps) with the product collected by filtration in >95% purity. Cyanoamides **22b** and **22c** were accessed in a similar manner from 4-chlorobenzylamine and 4-methylbenzylamine (Scheme 3).

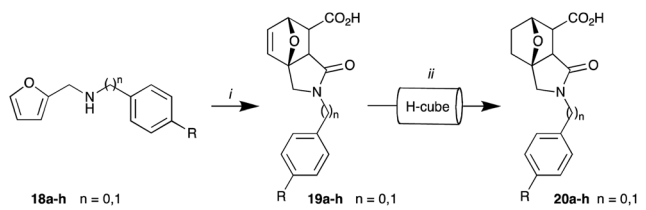
With **22a** we next investigated the potential selective reduction of the olefin and the nitrile moieties as outlined in Step 2, **Path B** (Fig. 3). Excluding possible debenzylation products, hydrogenation of **22a** had the potential to give seven different reduction products (**23a**, **25a–30a**) arising from various combinations of furan, olefin and nitrile moiety reductions (Scheme 5). Hence access to the analogues desired for subsequent focused library development was potentially a significant challenge.

A 0.05 M solution of **22a** was subjected to H-Cube conditions of 50 bar H_2 pressure, 50 °C, and a flow rate of 1 mL min^{-1} for 10 minutes using a 30 mm 10% Pd/C catcart™ (Scheme 5). Analysis showed quantitative reduction of the furan and olefin double bond moieties giving **28a** (Scheme 4 and Table 2). No nitrile reduction was observed.

Efforts to effect nitrile reduction using standard conditions (70 °C and 50 bar H_2 pressure‡) resulted only in clean conversion to **28a**. A similar outcome was noted with all optimisations with $T \geq 50$ °C regardless of the H_2 pressure (Table 2, entries 1–6). Easing of the reduction conditions (10 °C, 0 bar H_2



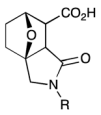
Scheme 1 *Reagents and conditions*: (i) H-Cube hydrogenation, 0.05 M **15** and 0.05 M **16a–h** (for details of R, see Table 1) in MeOH, 10% Pd/C, 50 °C, 50 bar H_2 pressure, 1 mL min^{-1}.

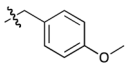
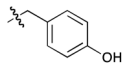
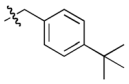
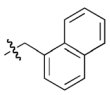
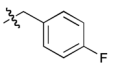
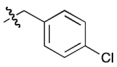
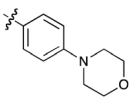


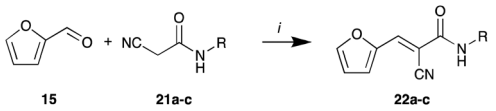
Scheme 2 *Reagents and conditions*: (i) diethyl ether, rt, 24 h; (ii) H-Cube, 0.05 M **20a** in MeOH, 10% Pd/C, 50 °C, 50 bar H_2 pressure, 1 mL min^{-1}.

‡ ThalesNano provide details of standard reducing conditions for a variety of functional groups: http://www.thalesNano.com.

Table 1 Synthesis of a focused library of isoindole-7-carboxylic acid analogues **20a–20h** by a combination of flow and batch chemistry approaches (**Path A**, Fig. 3)



Compound	R	Step 1 (%)	Step 2 (%)	Step 3 (%)	Overall (%)
20a		89	69	100	51
20b		85	66	88	47
20c		88	62	100	53
20d		84	44	100	37
20e		74	33	85	24
20f		82	46	100	38
20g		63	57	100	36
20h		76	40	100	30

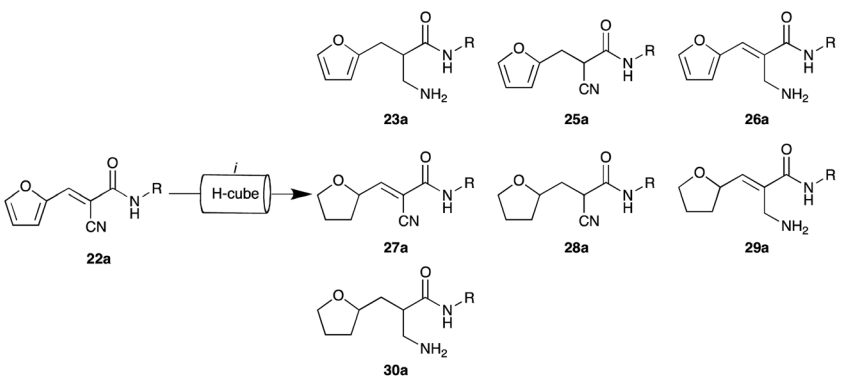


Scheme 3 *Reagents and conditions*: (i) EtOH, piperidine, 0.5 h, 25 °C.

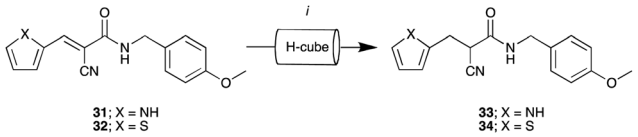
pressure) did show the first evidence of olefin *vs.* furan reduction selectivity with both the olefin reduction product (**25a**, 21%) and **28a** (79%) evident (Table 2, entry 17).

The production of **25a** suggested that **28a** resulted from over reduction of this compound. We believed that this is most likely related to catalyst residence time. Reducing residence time from 4 min (1 mL min^{-1}) to 3 min resulted in an improvement in the **25a : 28a** ratio to 64 : 36 (Table 3, entry 1). Further residence time reduction to 0.5 min saw clean generation of **25a** (Table 3, entry 4).

To examine whether this selective reduction could be performed on related heterocycles we investigated the pyrrole (**31**)



Scheme 4 *Reagents and conditions*: (i) H-Cube, 0.05 M **22a** (R = *p*-OCH_3PhCH_2–) in MeOH, 10% Pd/C, at 1 mL min^{-1} and the reduction products (**23a**, **25a–30a**) potentially obtainable by choice of hydrogenation conditions (see Table 2 for detail).



Scheme 5 *Reagents and conditions*: (i) 0.05 M **31** or **32** (MeOH), 10% Pd/C, 100 °C, 100 bar H_2, 1 mL min^{-1}, H-Cube™.

Table 2 Optimisation of temperature and H_2 pressure, for the reduction of **22a** to **25a** and **28a** and using a 10% Pd/C hydrogenation catalyst at 1.0 mL min^{-1} flow rate.[a] Reactions were conducted for 10 minutes and analysed using GC-MS

Entry	T (°C)	H_2 P (bar)	**25a** (%)	**28a** (%)
1	100	0	0	100
2	80	0	0	100
3	60	60	0	100
4	60	0	0	100
5	50	50	0	100
6	50	0	0	100
7	40	40	12	88
8	40	0	4	96
9	30	30	15	85
10	25	40	18	82
11	25	30	15	85
12	25	20	11	89
13	25	10	5	95
14	25	0	1	99
15	20	0	11	89
16	15	0	11	89
17	10	0	21	79

[a] 1 mL min^{-1} is equivalent to a 4 min residence time (http://www.thalesnano.com).

Table 3 Optimisation of the reduction of **22a** to **25a**. Reactions were conducted at flow rates of 1.33–8 mL min^{-1}, 25 °C, 0 bar, 10% H_2 and analysed using GC-MS

Entry	Catalyst	Residence time (min)	**25a** (%)	**28a** (%)
1	10% Pd/C	3.0	64	36
2	10% Pd/C	1.5	80	20
3	10% Pd/C	0.8	89	11
4	10% Pd/C	0.5	100	0

and thiophene (**32**) analogues of **22a** (Scheme 5). Analogues **31** and **32** were synthesised as per **22a** from pyrrole-2-carbaldehyde and thiophene-2-carbaldehyde respectively. In contrast to **22a**, both **31** and **32** showed exclusive reduction of the olefin moiety affording **33** and **34**, respectively. No change in this reduction was evident with **31** and **32** with reaction conditions of 100 °C and 100 bar H_2 pressure and once again no evidence of nitrile reduction was evident.

As no evidence of nitrile reduction was obtained using Pd/C, for any of the analogues examined thus far, we next conducted a rapid catalyst scan using **22a** as the model compound (Table 4). At 60 °C and 60 bar H_2 pressure the Pd-based catalysts gave

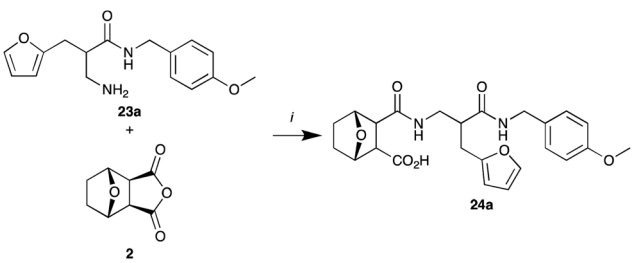
Table 4 Evaluation of hydrogenation catalysts for the selective reduction of **22a** to **23a**, **25a**, **28a** and **30a** at 1.0 mL min^{-1} flow rate, 60 °C, 60 bar H_2, unless otherwise indicated

Entry	Catalyst	**23a** (%)	**25a** (%)	**28a** (%)	**30a** (%)
1	10% Pd/C	0	10	90	0
2	20% $Pd(OH)_2/C$	0	4	96	0
3	Pd tetrakis	0	71	29	0
4	5% Pt/C (sulfided)	0	65	35	0
5	RuO_2	0	0	0	0
6	0.5% Ir/C	0	0	0	0
7	5% Re/C	0	0	0	0
8	Re_2O_7	0	0	0	0
9	RaNi	0	0	0	100
10	RaNi	91[a]	9	0	0

[a] Reaction conducted at 10 bar H_2 pressure, 50 °C and 1.0 mL min^{-1}.

varying ratios of **25a** and **28a**, with no evidence of the desired **23a** (Table 4, entries 1–4). Of the Pd-based catalysts both the 10% Pd–C and 20% $Pd(OH)_2$ showed preference for reduction of the furan and olefin moiety (Table 4, entries 1 and 2). The Pd tetrakis and 5% Pt/C (sulfided) showed *ca.* 2 : 1 preference for the formation of the olefin reduced **25a** over the furan and olefin reduced **28a** (Table 4, entries 3 and 4). While no evidence of the desired nitrile reduction was evident, these data suggest that further optimisation may afford exclusive access to both **25a** and **28a**. We observed no reduction products at 1.0 mL min^{-1}, 60 °C and 60 bar H_2 pressure with the RuO_2, 0.5% Ir/C, 5% Re/C or Re_2O_7 (Table 4, entries 5–8). However using the same conditions with RaNi we observed global reduction to **30a** (see Scheme 5). However repeating the RaNi reaction at 10 bar H_2 pressure and 50 °C reduced the olefin and nitrile moieties giving the desired **23a** (91%, Table 4 entry 10).

The RaNi reduction also proved compatible with a range of substituted pyrrole analogues allowing access to a series of novel amines for subsequent addition to norcantharidin (**2**) in the final step of **Path B**. Stirring in acetone at room temperature for 4 hours afforded the desired product 7-oxabiclcyo[2.2.1]-heptane **24a** in a 78% yield upon filtration of the crude reaction mixture (Scheme 6).[52] Pleasingly, as with reaction **Path A**, reaction **Path B** proved amenable to various functional group alterations and was utilised to access a small library of furan (Fig. 4, **24a–24c**) and pyrrole (**24d–24g**), and thiophene (**24h** and **24i**) based norcantharidin analogues.



Scheme 6 *Reagents and conditions*: (i) acetone, rt, 4 h.

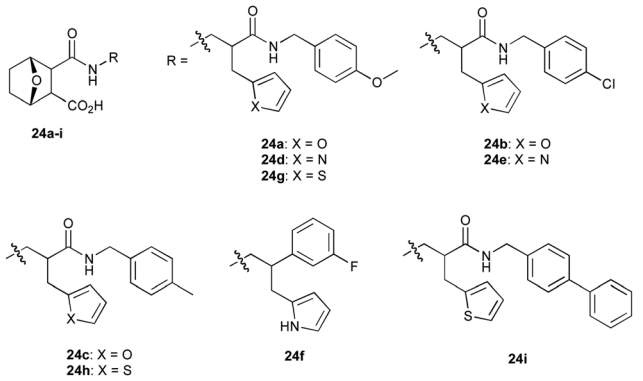
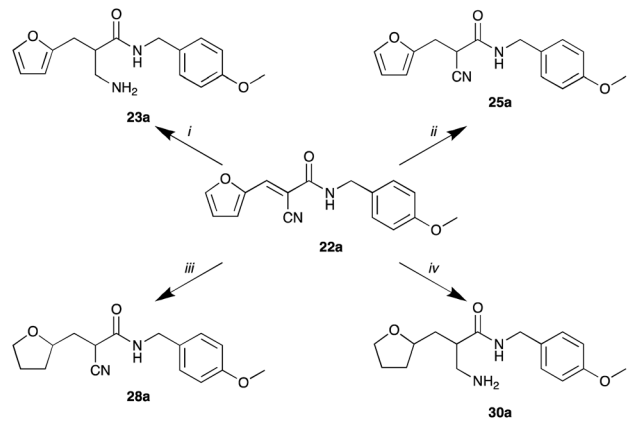


Fig. 4 Small library of analogues access by sequential flow reaction Path B including a number of furan (24a–24c), pyrrole (24d–24g), and thiophene (24h and 24i) based norcantharidin analogues.



Scheme 7 *Reagents and conditions*: (i) H-cube RANEY® Ni, 50 °C, 10 bar H_2, 1 mL min^{-1}; (ii) H-Cube Pd/C, 25 °C, 0 bar, 10% H_2, 3.0 mL min^{-1} (iii) H-Cube Pd/C, 50 °C, 50 bar H_2, 1 mL min^{-1}; (iv) H-cube RANEY® Ni, 60 °C, 60 bar H^2, 1.0 mL min^{-1}.

Conclusion

From the outset of this study we were aware that step 1 of **Path A**, reduction of the imine **17**, couple potentially could yield the desired reductive amination product (**18**, Fig. 3) or the equivalent tetrahydrofuran; and that Path B was likely to be more complex with the reduction of **22** potentially yielding seven reduction products (Scheme 5, plus additional debenzylation products). However by judicious choice of flow reduction reductive amination of **15** with a range of amines was effected at 50 °C, 50 bar H_2 pressure and 1.0 mL min^{-1} to give exclusively the reductive amination product **18**. Interestingly the same conditions with furan **22**, which could give rise to seven reduction products (excluding debenzylation), resulted in reduction only of the furan and olefin moieties with clean generation of **28**, suggesting that the amino/imine moieties of **18** drove affected the flow reduction outcomes. Reducing catalyst residence times from 4 min to 0.5 min allowed access to exclusively the furan olefin reduced product (**25**). Catalyst switching from Pd/C to RaNi and manipulation of the flow conditions to 50 °C, 10 bar and 1 mL min^{-1} allowed access to the desired furanyl amides (reduction of the olefin and nitrile moieties) (**23**) for subsequent synthesis of the desired 7-oxabicyclo[2.2.1]heptane carboxylic acid analogues (**24**).

With the desired amines in hand the Diels–Alder addition of **18** with maleic anhydride followed by an intramolecular lactamisation followed by a second flow reduction (of the resultant C=C) gave a focused library of isoindole-7-carboxylic acids (**20a–h**) in modest to good yields for the three steps. Importantly these products were access in 50–100 mg quantities through two flow chemistry (10 minute) and one batch reaction in >95% purity requiring no purification. Similarly, with **23** in hand, addition of norcantharidin (**2**) saw smooth conversion to the desired focused library of 7-oxabicyclo[2.2.1]heptane carboxylic acids (**24a–i**). In this instance analogues **24a–i** were rapidly accessed *via* a solvent free reaction, one 10 minute flow hydrogenation reaction and nucleophilic addition to the anhydride moiety of **2**. These analogues were isolated by filtration and/or trituration in 50–100 mg quantities in >95% purity.

Herein we have applied the principles of green chemistry where possible. The use of flow chemistry approaches has allowed reagent minimisation (10 mL of a 0.05 M solution) and rapid reaction optimisation. Careful control of residence times, temperature and H_2 pressure permitted exclusive reduction of **22** to **23a**, **26a** or **28a**, a level of control difficult to envisage under traditional batch hydrogenation approaches (Scheme 7). Batch reduction approaches typically only afford the global reduction products.[43–45] The high conversion rates minimised purification requirements typically to filtration and/or trituration. In instances were diethyl ether was the solvent of choice, the recovered solvent was directly for product trituration in subsequent steps. The combined use of flow an batch chemistry provided facile access to the two series of bicycle[2.2.1]heptane analogues, the isoindole-7-carboxylic acids (**20**) and the 7-oxabicyclo[2.2.1]0heptane carboxylic acids (**24**). We are currently developing an extended series of these analogues which will be assessed against a panel of human cancer cell lines and the results of these studies will be reported in due course.

We believe that with rapid reaction optimisation, reduced work-up and chromatography requirements, sequential flow methodologies integrated with batch chemistry has the potential to aid sustainable practices in medicinal chemistry.

Experimental

General experimental

All reagents were purchased from Sigma Aldrich and were used without purification, with the exception of furfural, which was distilled from glass prior to use. Solvents were bulk, and distilled from glass prior to use.

^1H and ^{13}C NMR spectra were recorded on a Brüker Advance™ AMX 400 MHz spectrometer at 400.1 and 100.1 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) measured to relative the internal standards. Coupling constants (J) are expressed in Hertz (Hz). Mass spectra were recorded on a Shimadzu LCMS 2010 EV using a mobile phase of 1 : 1 acetonitrile : H_2O with 0.1% formic acid. Gas chromatography-mass spectrometry (GC-MS) was performed on

a Shimadzu GC-MS QF2010 EI/NCI System equipped with a ZB-5MS capillary column of 5% phenylarylene stationary phase.

Melting points were recorded on a BUCHI Melting Point M-565. IR spectra were recorded on a PerkinElmer Spectrum Two™ FTIR Spectrometer. Thin layer chromatography (TLC) was performed on Merck 60 F_{254} pre-coated aluminium plates with a thickness of 0.2 mm. Column chromatography was performed under 'flash' conditions on Merck silica gel 60 (230–400 mesh). Microwave irradiations were conducted using a CEM Discover® Benchmate microwave, and hydrogenations were performed either using a ThalesNano H-Cube™ or a ThalesNano H-CubePro™ (H-Cube™) continuous-flow hydrogenation reactor. All reactions were passed through the H-Cube™ reactor once, unless otherwise specified.

General procedure 1 – direct reductive amination

1-(Furan-2-yl)-*N*-(4-methoxybenzyl)methanamine (18a). A solution of 4-methoxybenzylamine (**16a**) (0.08 mL, 0.6 mmol) and furan-2-carbaldehyde (**15**) (0.05 mL, 0.6 mmol) was diluted in MeOH (2.5 mL) to afford a 0.05 M solution which was subsequently hydrogenated with a H-Cube™ using a 10% Pd/C catalyst at 1 mL min^{-1} flow rate, 50 °C and 50 bar H_2 pressure. The eluate was concentrated *in vacuo* to afford **18a** as a yellow oil (0.12 g, 89%).

GC-MS 4.06 r.t.; LRMS (ESI^+) *m*/*z* 218 (M + 1). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, $J = 1.1$ Hz, 1H), 7.35 (d, $J = 8.6$ Hz, 2H), 6.92 (d, $J = 8.6$ Hz, 2H), 6.38 (dd, $J = 2.0$, 1.2 Hz, 1H), 6.27 (d, $J = 3.2$ Hz, 1H), 3.84 (s, 3H), 3.70 (s, 2H), 3.61 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.7, 152.6, 142.0, 130.9, 130.2, 113.7, 110.1, 108.8, 56.5, 55.3, 49.2. IR (cm^{-1}) 3330 (NH), 2960, 2763 (CH), 1615, 1513 (C═C), 1463, 1432 (CH_2), 1247 (CH_3), 1218 (C–O), 830 (*p*-C Ph).

***N*-Benzyl-1-(furan-2-yl)methanamine (18b).** Synthesised as described in general procedure 1 from benzylamine (**16b**) and furan-2-carbaldehyde (**15**).

LRMS (ESI^+) *m*/*z* 188 (M + 1). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30 (dd, $J = 4.2$, 3.3 Hz 1H), 7.23 (d, $J = 4.1$, Hz, 2H), 7.19–7.11 (m, 1H), 6.24–6.22 (m, 1H), 6.14 (d, $J = 3.1$ Hz, 1H), 3.70 (s, 1H), 3.58 (s, 2H), 3.53 (s, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 152.5, 142.1, 129.0, 128.5, 128.3, 127.0, 110.1, 108.8, 57.1, 49.4. IR (cm^{-1}) 3330 (NH), 2976, 2929, 2838 (CH), 1602, 1507 (C═C), 1453, 1360 (CH_2).

4-((Furan-2-ylmethylamino)methyl)phenol (18c). Synthesised as described in general procedure 1 from 4-hydroxybenzylamine (**16c**) and furan-2-carbaldehyde (**15**).

LRMS (ESI^+) *m*/*z* 204 (M + 1). ^1H NMR (MeOD, 400 MHz): δ 7.49 (d, $J = 1.0$ Hz, 1H), 7.19 (d, $J = 8.4$ Hz, 1H), 6.76 (d, $J = 8.5$ Hz, 1H), 6.40–6.38 (m, 1H), 6.30 (d, $J = 3.0$ Hz, 1H), 3.62 (s, 2H), 3.51 (s, 1H), 3.33 (s, 1H). ^{13}C NMR (MeOD, 101 MHz): δ 156.3, 152.0, 141.9, 130.2, 128.9, 114.6, 109.8, 108.8, 56.3, 48.4. IR (cm^{-1}) 3290 (OH), 2963, 2923, 2858 (CH), 1613, 1514 (C═C), 1448, 1360 (CH_2), 1225 (C–O), 819 (*p*-C Ph).

***N*-(4-*tert*-Butylbenzyl)-1-(furan-2-yl)methanamine (18d).** Synthesised as described in general procedure 1 from 4-*tert*-butylbenzylamine (**16d**) and furan-2-carbaldehyde (**15**).

LRMS (ESI^+) *m*/*z* 244 (M + 1). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.33 (m, 3H), 7.25 (d, $J = 8.3$ Hz, 2H), 6.31 (dd, $J = 3.1$, 1.9 Hz, 1H), 6.18 (d, $J = 3.1$ Hz, 1H), 3.79 (s, 2H), 3.76 (s, 2H), 1.31 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 154.0, 149.9, 141.8, 137.0, 128.0, 125.3, 125.3, 110.1, 107.0, 52.5, 45.5, 34.5, 31.4. IR (cm^{-1}) 3330 (NH), 2961, 2904, 2868 (CH), 1597, 1508 (C═C), 1460, 1362 (CH_2), 1269 (CH_3), 804 (*p*-C Ph).

1-(Furan-2-yl)-*N*-(naphthalen-1-ylmethyl)methanamine (18e). Synthesised as described in general procedure 1 from 1-naphthylamine (**16e**) and furan-2-carbaldehyde (**15**).

LRMS (ESI^+) *m*/*z* 238 (M + 1). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, $J = 8.2$ Hz, 1H), 7.88–7.84 (m, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.52–7.40 (m, 5H), 6.35 (dd, $J = 3.1$, 1.9 Hz, 1H), 6.24 (d, $J = 3.2$ Hz, 1H), 4.23 (s, 2H), 3.89 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 153.9, 141.9, 135.5, 133.9, 131.9, 128.7, 127.9, 126.3, 126.2, 125.6, 125.4, 123.6, 110.2, 107.2, 50.4, 45.9. IR (cm^{-1}) 3321 (NH), 3047, 2925, 2832, (CH), 1597, 1508 (C═C), 1450, 1396 (CH_2), 790 (*p*-C Ph).

***N*-(4-Fluorobenzyl)-1-(furan-2-yl)methanamine (18f).** Synthesised as described in general procedure 1 from 4-fluorobenzylamine (**16f**) and furan-2-carbaldehyde (**15**).

LRMS (ESI^+) *m*/*z* 206 (M + 1). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37 (d, $J = 1.0$ Hz, 1H), 7.30–7.27 (m, 2H), 6.99 (d, $J = 8.7$ Hz, 2H), 6.32 (dd, $J = 3.1$, 1.9 Hz, 1H), 6.18 (d, $J = 3.1$ Hz, 1H), 3.77 (s, 2H), 3.75 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.0 (d, $J = 245.5$ Hz), 152.3, 142.1, 130.5, 130.4, 115.2, 115.0, 110.1, 108.9, 56.3, 49.3. IR (cm^{-1}) 3317 (NH), 2971, 2925, 2836, (CH), 1602, 1507 (C═C), 1416, 1358 (CH_2), 1009 (F–C Ph), 821 (*p*-C Ph).

***N*-(4-Chlorobenzyl)-1-(furan-2-yl)methanamine (18g).** Synthesised as described in general procedure 1 from 4-chlorobenzylamine (**18g**) and furan-2-carbaldehyde (**15**).

LRMS (ESI^+) *m*/*z* 222 (M + 1). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41 (d, $J = 1.1$ Hz, 1H), 7.36–7.25 (m, 4H), 6.34 (dd, $J = 3.1$, 1.9 Hz, 1H), 6.23 (d, $J = 3.1$ Hz, 1H), 3.77 (d, $J = 9.2$ Hz, 1H), 3.66 (s, 2H), 3.58 (s, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ IR (cm^{-1}) 3312 (NH), 2921, 2777, 22730 (CH), 1601, 1573 (C═C), 1452, 1428 (CH_2), 810 (*p*-C Ph), 599 (Cl–C Ph).

***N*-(Furan-2-ylmethyl)-4-morpholinoaniline (18h).** Synthesised as described in general procedure 1 from 4-morpholinoaniline (**16h**) and furan-2-carbaldehyde (**15**).

LRMS (ESI^+) *m*/*z* 259 (M + 1). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36 (d, $J = 1.1$ Hz, 1H), 6.84 (d, $J = 8.9$ Hz, 2H), 6.66 (d, $J = 8.9$ Hz, 2H), 6.31 (dd, $J = 3.1$, 1.9 Hz, 1H), 6.21 (d, $J = 2.8$ Hz, 1H), 4.28 (s, 2H), 3.85 (t, $J = 4.5$ Hz, 4H), 3.02 (t, $J = 4.6$ Hz, 4H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 153.0, 144.1, 142.1, 141.9, 118.2, 114.4, 110.3, 106.9, 67.1, 51.1, 42.2. IR (cm^{-1}) 3395 (NH), 2964, 2851, 2824 (CH), 1615 (C═C), 1512 (O═C–N), 1458, 1408 (CH_2), 1220 (C–O), 1117 (C–O), 918 (C═C bend) 824 (*p*-C Ph).

General procedure 2 – reaction path A

2-[(4-Dimethoxyphenyl)methyl]octahydro-1-oxo-3*a*,6-epoxy-3*aH*-isoindole-7-carboxylic acid (20a). 1-(Furan-2-yl)-*N*-(4-methoxybenzyl)methanamine **18a** 0.12 g, 0.51 mmol and maleic anhydride (0.06 g, 0.61 mmol) were dissolved separately in diethyl ether (10 mL × 2) and the solutions were added together and the reaction was left to stir at room temperature overnight. The solution was filtered and washed with cold diethyl ether and dried under suction to afford **20a** as a yellow solid. The crude product was then dissolved in acetone (6 mL) to form a

~0.05 M solution. This solution was hydrogenated using the H-Cube™ with a 10% Pd/C catalyst at 1 mL min^{-1} flow rate, 50 °C and 50 bar H_2 pressure. The eluate was concentrated *in vacuo* and then triturated with ether to afford **20a** as a pale orange solid; 0.1 g, overall 51%; mp 115–116 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (s, 1H), 7.20 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.87 (d, J = 5.6 Hz, 1H), 4.52 (d, J = 14.8 Hz, 1H), 4.42 (d, J = 14.8 Hz, 1H), 3.80 (s, 3H), 3.62 (d, J = 11.8 Hz, 1H), 3.53 (d, J = 11.8 Hz, 1H), 3.21–3.13 (m, 2H), 1.97 (dt, J = 13.3, 6.9 Hz, 1H), 1.79–1.69 (m, 2H), 1.64–1.55 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.9, 159.2, 129.4, 127.4, 114.3, 86.3, 79.9, 55.3, 54.4, 52.4, 48.7, 46.4, 29.5, 29.1. IR (cm^{-1}) 3592 (N), 3528 (OH), 2983, 2955, 2892, 2834 (CH), 1730 (CO), 1644 (CO), 1612 (C=C), 1513 (O=C–N), 1473, 1422 (CH_2), 1355 (CH_3), 1173 (C–O), 842 (*p*-C Ph).

2-(Phenylmethyl)octahydro-1-oxo-3*a*,6-epoxy-3*aH*-isoindole-7-carboxylic acid (20b). Synthesised as described in general procedure 2 – sequential reaction Path A from **18b** and maleic anhydride to afford **20b** as a pale orange solid; 0.07 g, overall yield 47%; mp 198–202 °C.

MS (ESI$^+$) m/z 288 (M + 1). ^{1}H NMR (MeOD, 400 MHz): δ 7.37–7.28 (m, 5H), 4.70 (d, J = 5.6 Hz, 1H), 4.58 (d, J = 15.2 Hz, 1H), 4.42 (d, J = 15.1 Hz, 1H), 3.63 (d, J = 11.7 Hz, 1H), 3.55 (d, J = 11.7 Hz, 1H), 3.19 (d, J = 9.6 Hz, 1H), 3.09 (d, J = 9.6 Hz, 1H), 2.00–1.90 (m, 1H), 1.84 (td, J = 11.3, 7.2 Hz, 1H), 1.76–1.66 (m, 2H). ^{13}C NMR (MeOD, 101 MHz): δ 173.6, 173.0, 135.9, 128.3, 127.5, 127.2, 86.3, 79.8, 54.0, 51.6, 48.3, 45.9, 29.0, 28.6. IR (cm^{-1}) 3378 (OH), 2972, 2935, 2878 (CH), 1713 (CO), 1685 (CO), 1652 (C=C), 1474, 1428 (CH_2), 1259 (C–O), 1163 (C–O).

2-[(4-Phenol)methyl]octahydro-1-oxo-3*a*,6-epoxy-3*aH*-isoindole-7-carboxylic acid (20c). Synthesised as described in general procedure 2 – sequential reaction Path A from **18c** and maleic anhydride to afford **20c** as a yellow solid, 0.1 g, overall 53%; mp 278–279 °C.

LRMS (ESI$^+$) m/z 304 (M + 1). ^{1}H NMR (DMSO, 400 MHz): δ 11.71 (s, OH), 9.33 (s, NH), 7.05 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 4.56 (d, J = 4.8 Hz, 1H), 4.31 (d, J = 14.9 Hz, 1H), 4.21 (d, J = 14.9 Hz, 1H), 3.48 (d, J = 11.5 Hz, 1H), 3.38 (d, J = 11.5 Hz, 1H), 3.07 (d, J = 9.7 Hz, 1H), 2.86 (d, J = 9.7 Hz, 1H), 1.73 (dd, J = 11.6, 5.3 Hz, 2H), 1.56 (t, J = 10.4 Hz, 2H). ^{13}C NMR (DMSO, 101 MHz): δ 172.7, 171.6, 157.0, 129.3, 127.1, 115.7, 86.1, 79.2, 53.9, 51.7, 48.2, 45.3, 29.6, 29.0. IR (cm^{-1}) 3257 (OH), 2979, 2955, 2950 (CH), 1713 (CO), 1650 (CO), 1620 (C=C), 1437, 1422 (CH_2), 1261 (CO), 1162 (CO), 822 (*p*-C Ph).

2-[(4-*tert*-Butylphenyl)methyl]octahydro-1-oxo-3*a*,6-epoxy-3*aH*-isoindole-7-carboxylic acid (20d). Synthesised as described in general procedure 2 – sequential reaction path A from **18d** and maleic anhydride to afford **20d** as a white solid, 0.2 g, overall yield 37%; mp 195–197 °C.

LRMS (ESI$^+$) m/z 338 (M + 1). ^{1}H NMR (MeOD, 400 MHz): δ 7.40 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 4.69 (d, J = 5.6 Hz, 1H), 4.51 (d, J = 15.0 Hz, 1H), 4.41 (d, J = 15.0 Hz, 1H), 3.61 (d, J = 11.7 Hz, 1H), 3.55 (d, J = 11.7 Hz, 1H), 3.17 (d, J = 9.6 Hz, 1H), 3.08 (d, J = 9.6 Hz, 1H), 1.97–1.90 (m, 1H), 1.87–1.80 (m, 1H), 1.70 (ddd, J = 10.7, 9.1, 4.3 Hz, 2H), 1.32 (s, 9H). ^{13}C NMR (MeOD, 101 MHz): δ 173.8, 172.9, 150.2, 132.9, 127.3, 125.2, 86.2, 79.8, 54.0, 51.7, 48.3, 45.6, 33.9, 30.4, 29.0, 28.6. IR (cm^{-1}) 3250 (OH), 2967, 2870 (CH), 1748 (CO), 1674 (CO), 1656 (C=C), 1475, 1409 (CH_2), 1401, 1389, 1354 (CH_3), 1269 (CO), 1148 (CO), 840 (*p*-C Ph).

2-[(Napthalen-1-yl)methyl]octahydro-1-oxo-3*a*,6-epoxy-3*aH*-isoindole-7-carboxylic acid (20e). Synthesised as described in general procedure 2 – sequential reaction Path A from **18e** and maleic anhydride to afford **20e** as an off white solid, 0.1 g, overall yield 30%; mp 212–213 °C.

LRMS (ESI$^+$) m/z 338 (M + 1). ^{1}H NMR (MeOD, 400 MHz): δ 8.09 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.57–7.44 (m, 4H), 5.01 (d, J = 15.1 Hz, 1H), 4.86 (d, J = 15.1 Hz, 1H), 4.67 (d, J = 5.6 Hz, 1H), 3.53 (d, J = 11.8 Hz, 1H), 3.44 (d, J = 11.8 Hz, 1H), 3.16 (d, J = 9.6 Hz, 1H), 3.07 (d, J = 9.6 Hz, 1H), 1.93–1.83 (m, 1H), 1.79–1.71 (m, 1H), 1.68–1.58 (m, 2H). ^{13}C NMR (MeOD, 101 MHz): δ 173.5172.5, 134.0, 131.4, 131.2, 128.3, 128.3, 126.5, 126.2, 125.6, 125.0, 123.2, 86.2, 79.8, 54.1, 51.6, 48.4, 44.2, 28.9, 28.5. IR (cm^{-1}) 3480 (OH), 3060, 3044, 2999, 2983, 2939 (CH), 1732 (CO), 1649 (CO), 1612 (C=C), 1485, 1425 (CH_2), 1264 (C–O), 1232 (C–O), 794(*m*-C Ph), 782 (*o*-C Ph).

2-[(4-Fluorophenyl)methyl]octahydro-1-oxo-3*a*,6-epoxy-3*aH*-isoindole-7-carboxylic acid (20f). Synthesised as described in general procedure 2 – sequential reaction Path A from **18f** and maleic anhydride to afford **20f** as a pale yellow solid, 0.15 g, overall yield 38%; mp 233–239 °C.

LRMS (ESI$^+$) m/z 306 (M + 1). ^{1}H NMR (MeOD, 400 MHz): δ 7.34 (dd, J = 8.7, 5.4 Hz, 2H), 7.07 (t, J = 8.8 Hz, 2H), 4.69 (d, J = 5.6 Hz, 1H), 4.61 (d, J = 15.2 Hz, 1H), 4.35 (d, J = 15.2 Hz, 1H), 3.64 (d, J = 11.7 Hz, 1H), 3.54 (d, J = 11.7 Hz, 1H), 3.18 (d, J = 9.6 Hz, 1H), 3.09 (d, J = 9.6 Hz, 1H), 1.95 (dd, J = 5.6, 3.6 Hz, 1H), 1.89–1.79 (m, 1H), 1.77–1.65 (m, 2H). ^{13}C NMR (MeOD, 101 MHz): δ 173.6, 173.0, 162.3 (d, J = 245.1 Hz), 132.0, 129.4, 129.3, 115.1, 114.8, 86.3, 79.8, 53.9, 51.6, 48.1, 45.1, 29.0, 28.6. IR (cm^{-1}) 3390 (OH), 3003, 2979, 2955, 2894 (CH), 1726 (CO), 1682 (CO), 1508 (C=C), 1436, 1415 (CH_2), 1262 (C–O), 1219 (C–O), 1003 (F–C Ph), 841 (*p*-C Ph).

2-[(4-Chlorophenyl)methyl]octahydro-1-oxo-3*a*,6-epoxy-3*aH*-isoindole-7-carboxylic acid (20g). Synthesised as described in general procedure 2 – sequential reaction Path A from **18g** and maleic anhydride to afford **20g** as a brown solid 0.1 g, overall yield 36%; mp 198–202 °C.

LRMS (ESI$^+$) m/z 322 (M + 1). ^{1}H NMR (MeOD, 400 MHz): δ 7.24–7.15 (m, 4H), 4.57 (d, J = 5.6 Hz, 1H), 4.50 (d, J = 15.4 Hz, 1H), 4.20 (d, J = 15.4 Hz, 1H), 3.52 (d, J = 11.7 Hz, 1H), 3.42 (d, J = 11.7 Hz, 1H), 3.06 (d, J = 9.6 Hz, 1H), 2.96 (d, J = 9.6 Hz, 1H), 1.87–1.77 (m, 1H), 1.76–1.68 (m, 1H), 1.64–1.53 (m, 2H). ^{13}C NMR (MeOD, 101 MHz): δ 173.5, 173.0, 134.8, 132.9, 129.0, 128.4, 86.3, 79.8, 53.9, 51.6, 48.3, 45.1, 29.0, 28.6. IR (cm^{-1}) 3439 (NH), 3322 (OH), 2975, 2906 (CH), 1721 (CO), 1659 (CO), 1489, 1426 (CH_2), 1275 (C–O), 1215 (C–O), 841 (*p*-C Ph), 567 (Cl–C Ph).

2-[(4-Morpholinaniline)methyl]octahydro-1-oxo-3*a*,6-epoxy-3*aH*-isoindole-7-carboxylic acid (20h). Synthesised as described in general procedure 2 – sequential reaction Path A from **18h** and maleic anhydride to afford **20h** as an off white solid, 0.1 g, overall 24%; mp 238–240 °C.

LRMS (ESI$^+$) m/z 359 (M + 1). ^{1}H NMR (DMSO-*d*,[6] 400 MHz): δ 12.06 (s, OH), 7.49 (d, J = 9.1 Hz, 2H), 6.93 (d, J = 9.2 Hz, 2H), 4.59 (d, J = 5.1 Hz, 1H), 4.15 (d, J = 11.5 Hz, 1H), 3.90 (d, J =

11.4 Hz, 1H), 3.76–3.70 (m, 4H), 3.26 (d, J = 9.7 Hz, 1H), 3.10–3.04 (m, 4H), 2.93 (d, J = 9.7 Hz, 1H), 1.88–1.73 (m, 2H), 1.74–1.55 (m, 2H). ^{13}C NMR (MeOD, 101 MHz): δ 171.8, 169.9, 147.0, 131.2, 119.8, 114.5, 84.2, 78.4, 65.5, 54.0, 51.1, 49.0, 48.1, 28.5, 27.9. IR (cm^{-1}) 3300 (OH), 2999, 2955, 2922, 2882 (CH), 1740 (CO), 1689 (CO), 1606 (C=C), 1511 (O=C–N), 1455, 1394 (CH_2), 1210 (C–O), 1170 (C–O), 824 (*p*-C Ph).

General procedure 3 – Knoevenagel condensation

2-Cyano-3-(furan-2-yl)-N-(4-methoxybenzyl)acrylamide (22a). 2-Cyano-*N*-(4-methoxybenzyl)acetamide (**21a**) was synthesised by stirring methyl cyanoacetate (1.50 g, 15.1 mmol) with 4-methoxybenzylamine (2.08 g, 15.1 mmol) in MeOH at room temperature for 60 min. After this time the solution was filtered and washed with cold MeOH and dried under suction to afford **21a** as a white solid; 70%; mp 136–138 °C. This material was used directly for the synthesis of **22a**.

LRMS (ESI$^+$) m/z 205 (M + 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 6.45 (s, 1H), 4.41 (d, J = 5.5 Hz, 2H), 3.82 (s, 3H), 3.39 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 160.7, 159.4, 129.4, 128.9, 114.7, 114.3, 55.3, 43.9, 25.9. IR (cm^{-1}) 3284 (NH), 3073, 2939, 2841 (CH), 2258 (CN), 1640 (CO), 1614, 1515 (C=C), 1515 (NH bend), 1462 (CH_2), 1368 (CH_3), 1240 (CO), 1031 (C–O–C), 815 (*p*-C Ph).

Furan-2-carboxaldehyde (**15**) (0.11 g, 1.2 mmol) and 2-cyano-*N*-(4-methoxybenzyl)acetamide (**21a**) (0.24 g, 1.2 mmol) were added together in EtOH (4 mL). Piperidine (cat.) was added and the reaction was left to stir at room temperature for 30 min and then placed in the freezer for 60 min. The solution was filtered and washed with cold EtOH and dried under suction to afford **22a** as an orange solid, 71%; mp 119–121 °C. GC–MS (r.t.) 15.46 min.

LRMS (ESI$^+$) m/z 283 (M + 1). ^{1}H NMR (acetone, 400 MHz): δ 8.04 (s, 1H), 7.96 (d, J = 1.4 Hz, 1H), 7.92 (br s, NH), 7.38 (d, J = 3.6 Hz, 1H), 7.31 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.78 (dd, J = 3.5, 1.7 Hz, 1H), 4.50 (d, J = 6.0 Hz, 1H), 3.78 (s, 3H), ^{13}C NMR (acetone, 101 MHz): δ 160.3, 159.1, 149.2, 148.0, 136.2, 131.0, 129.1, 120.7, 115.9, 113.7, 113.6, 101.1, 54.6, 43.1. IR (cm^{-1}) 3323 (NH), 3128, 3038, 3006, 2833 (CH), 2226 (CN), 1657 (CO), 1605 (C=C), 1532 (NH bend), 1436 (CH_2), 1351 (CH_3), 1298 (C–O), 1244 (C–O), 1029 (C–O–C), 826 (*p*-C Ph).

2-Cyano-3-(furan-2-yl)-*N*-(4-chlorobenzyl)acrylamide (22b). 2-Cyano-*N*-(4-chlorobenzyl)acetamide (**21b**) was synthesised by adding together methyl cyanoacetate (0.5 g, 5.1 mmol) with 4-chlorobenzylamine (0.71 g, 5.1 mmol) in EtOH (4 mL). Piperidine (cat.) was added and the reaction was irradiated with microwaves (120 °C, 200 W) for 15 min and then placed in the freezer for 60 min. The solution was filtered and washed with cold EtOH and dried under suction to afford to afford **21b** as a pale yellow solid, 50%; mp 131–133 °C. This material was used directly for the synthesis of **22b**.

LRMS (ESI$^+$) m/z 209 (M + 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.27 (m, 2H), 7.22 (d, J = 8.5 Hz, 2H), 6.47 (s, 1H), 4.44 (d, J = 5.8 Hz, 2H), 3.41 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 160.8, 135.3, 134.0, 129.3, 129.1, 114.6, 43.7, 25.9. IR (cm^{-1}) 3281 (NH), 3083, 2965, 2919 (CH), 1648 (CO), 1565 (C=C), 1456 (CH_2), 1220 (C–O), 1204 (C–O), 804 (*p*-C Ph), 533 (Cl–C Ph).

Furan-2-carboxaldehyde (**15**) and 2-cyano-*N*-(4-chlorobenzyl) acetamide (**21b**) were reacted as described in general procedure 3 to afford **22b** as an orange solid 67%; mp 149–151 °C.

LRMS (ESI$^+$) m/z 287 (M + 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (s, 1H), 7.73 (d, J = 1.6 Hz, 1H), 7.35–7.31 (m, 2H), 7.27–7.25 (m, 2H), 7.20 (d, J = 3.6 Hz, 1H), 6.64 (dd, J = 3.6, 1.7 Hz, 2H), 4.56 (d, J = 5.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 160.4, 148.9, 147.9, 137.7, 135.8, 133.8, 129.2, 129.0, 121.4, 116.7, 113.6, 99.5, 43.8. IR (cm^{-1}) 3375 (NH), 3115, 3036, (CH), 2211 (CN), 1668 (CO), 1610 (C=C), 1540 (NH bend), 1463 (CH_2), 1283 (C–O), 1253 (C–O), 1022 (C–O–C), 826 (*p*-C Ph), 591 (Cl–C Ph).

2-Cyno-3-(furan-2-yl)-N-(4-methylbenzyl)acrylamide (22c). 2-Cyano-*N*-(4-methylbenzyl)acetamide (**21c**) was synthesised by stirring methyl cyanoacetate (0.72 g, 7.3 mmol) with 4-methylbenzylamine (0.88 g, 7.3 mmol) at room temperature for 60 min. After this time the solid was recrystallized from EtOH to afford **21c** as a white solid, 42%; mp 132–134 °C. This material was used directly for the synthesis of **22c**.

LRMS (ESI$^+$) m/z 287 (M + 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 (s, 4H), 6.34 (s, 1H), 4.43 (d, J = 5.6 Hz, 2H), 3.38 (s, 2H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 160.6, 137.9, 133.7, 129.6, 128.0, 114.6, 44.2, 25.8, 21.1. IR (cm^{-1}) 3289 (NH), 3058, 2928 (CH), 2261 (CN), 1644 (CO), 1545 (C=C), 1517 (NH bend), 1463 (CH_2), 1364 (CH_3), 1229 (C–O), 1062 (C–O–C), 809 (*p*-C Ph).

Furan-2-carboxaldehyde (**15**) and 2-cyano-*N*-(4-methylbenzyl) acetamide (**21c**) were reacted as described in general procedure 3 to afford **22c** as a white solid, 50%; mp 130–132 °C.

LRMS (ESI$^+$) m/z 267 (M + 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (s, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.19 (dt, J = 8.0, 3.7 Hz, 4H), 6.62 (dd, J = 3.6, 1.7 Hz, 1H), 6.57 (s, 1H), 4.55 (d, J = 5.7 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 160.2, 149.0, 147.7, 137.7, 137.5, 134.1, 129.6, 127.9, 121.1, 116.7, 113.5, 99.8, 44.4, 21.1. IR (cm^{-1}) 3327 (NH), 3117, 3037 (CH), 2225 (CN), 1655 (CO), 1604, 1531 (C=C), 1512 (NH bend), 1425 (CH_2), 1392 (CH_3), 1261 (C–O), 1016 (C–O–C), 810 (*p*-C Ph).

2-Cyano-3-(pyrrole-2-yl)-*N*-(4-methoxybenzyl)acrylamide (31). Pyrrole-2-carboxaldehyde (0.10 g, 1.0 mmol) and 2-cyano-*N*-(4-methoxybenzyl)acetamide (**21a**) (0.21 g, 1.0 mmol) were added together in EtOH (4 mL). Piperidine (cat.) was added and the reaction was irradiated with microwaves (120 °C, 200 W) for 45 min and then placed in the freezer for 60 min. The solution was filtered and washed with cold EtOH and dried under suction to afford **31** as an orange solid; 93%; mp 204–208 °C.

GC-MS (r.t.) 19.08 min. LRMS (ESI$^+$) m/z 282 (M + 1). ^{1}H NMR (acetone, 400 MHz): δ 8.07 (s, 1H), 7.38 (d, J = 3.5 Hz, 1H), 7.27 (d, J = 8.5 Hz, 2H), 7.22 (s, 1H), 6.90 (d, J = 8.6 Hz, 2H), 6.49–6.38 (m, 1H), 4.45 (s, 2H), 3.79 (s, 3H) ^{13}C NMR (Acetone, 101 MHz): δ 163.2, 159.0, 140.3, 130.6, 128.5, 126.7, 126.3, 117.2, 117.2, 113.5, 112.29, 93.9, 54.3, 42.8. IR (cm^{-1}) 3360 (NH), 3089, 3008, 2936 (CH), 2202 (CN), 1647 (CO), 1611, 1550 (C=C), 1510 (NH bend), 1426 (CH_2), 1395 (CH_3), 1254 (C–O), 1050 (C–O–C), 821 (*p*-C Ph).

2-Cyano-3-(pyrrole-2-yl)-N-(4-chlorobenzyl)acrylamide (22d). Pyrrole-2-carboxaldehyde and 2-cyano-*N*-(4-chlorobenzyl)acetamide (**21b**) were reacted as described in general procedure 3 to afford **22d** as a white solid; 78%; mp 230–232 °C.

LRMS (ESI^+) *m/z* 286 (M + 1). ^1H NMR (DMSO, 400 MHz): δ 11.90 (s, NH), 8.68 (t, J = 5.9 Hz, 1H), 8.07 (s, 1H), 7.45–7.33 (m, 2H), 7.33–7.29 (m, 3H), 6.42 (dd, J = 3.5, 2.6 Hz, 1H), 4.37 (d, J = 6.0 Hz, 2H). ^{13}C NMR (DMSO, 101 MHz): δ 162.4, 140.8, 138.8, 131.8, 129.7, 128.7, 127.0, 126.8, 118.2, 116.1, 113.1, 94.9, 42.9. IR (cm^{-1}) 3349 (NH), 3097, 3025, 2971 (CH), 2205 (CN), 1645 (CO), 1574, 1524 (C=C), 1490 (NH bend), 1421 (CH_2), 1231 (C–O), 1012 (C–O–C), 810 (*p*-C Ph), 557 (Cl–C Ph).

2-(3-Fluorophenyl)-3-(1*H*-pyrrol-2-yl)acrylonitrile (22e). Pyrrole-2-carboxaldehyde (0.2 g, 2.1 mmol) and 3-fluorophenylacetonitrile (0.24 g, 2.1 mmol) were added together in EtOH (4 mL). Piperidine (cat.) was added and the reaction was irradiated with microwaves (120 °C, 200 W) for 20 min and then placed in the freezer for 60 min. The solution was filtered and washed with cold EtOH and dried under suction to afford **22e** as a yellow solid; 70%; mp 99–100 °C.

LRMS (ESI^+) *m/z* 213 (M + 1). ^1H NMR ($CDCl_3$, 400 MHz): δ 9.72 (br s, NH), 7.33–7.28 (m, 2H), 7.22–7.18 (m, 2H), 7.02 (d, J = 1.2 Hz, 1H), 6.99–6.90 (m, 1H), 6.65 (t, J = 3.7 Hz, 1H), 6.32–6.26 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.5, 136.3, 131.9, 127.5, 124.6, 120.8, 119.9, 115.1, 114.9, 111.9, 111.7, 111.1, 100.1. IR (cm^{-1}) 3330 (NH), 3028, 2972 (CH), 2220 (CN), 1608, 1542 (C=C), 1512 (NH bend), 1050 (F–C Ph), 759 (*m*-C Ph).

2-Cyano-3-(thiophene-2-yl)-*N*-(4-methoxybenzyl)acrylamide (32). Thiophene-2-carboxaldehyde (0.12 g, 1.0 mmol) and 2-cyano-*N*-(4-methoxybenzyl)acetamide (**21a**) (0.21 g, 1.0 mmol) were added together in EtOH (4 mL). Piperidine (cat.) was added and the reaction was irradiated with microwaves (120 °C, 200 W) for 45 min and then placed in the freezer for 60 min. The solution was filtered and washed with cold EtOH and dried under suction to afford **32** as an orange solid; 93%; mp 137–138 °C.

GC-MS (r.t.) 8.19 min. LRMS (ESI^+) *m/z* 299 (M + 1). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.44 (s, 1H), 8.01 (d, J = 5.0 Hz, 1H), 7.91 (d, J = 3.5 Hz, 1H), 7.31 (dd, J = 8.6, 3.7 Hz, 3H), 6.89 (d, J = 8.7 Hz, 2H), 4.51 (d, J = 5.8 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 160.3, 159.1, 143.8, 137.2, 136.4, 134.1, 131.0, 129.1, 128.4, 116.3, 113.7, 101.8, 54.6, 43.1. IR (cm^{-1}) 3333 (NH), 3106, 3074, 2836 (CH), 2220 (CN), 1655 (CO), 1615, 1534 (C=C), 1512 (NH bend), 1415 (CH_2), 1320 (CH_3), 1249 (C–O), 1031 (C–O–C), 797 (*p*-C Ph).

2-Cyano-3-(thiophene-2-yl)-*N*-(4-methylbenzyl)acrylamide (22f). Pyrrole-2-carboxaldehyde and 2-cyano-*N*-(4-methylbenzyl)acetamide (**21c**) were reacted as described in general procedure 3 to afford **22f** as an orange solid; 78%; mp 149–151 °C.

LRMS (ESI^+) *m/z* 283 (M + 1). ^1H NMR $CDCl_3$, 400 MHz: δ 8.46 (s, 1H), 7.74 (dd, J = 12.2, 4.4 Hz, 2H), 7.22–7.15 (m, 4H), 6.51 (s, 1H), 4.55 (d, J = 5.7 Hz, 2H), 2.35 (s, 2H), 1.56 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 160.4, 145.0, 137.7, 136.5, 136.4, 134.2, 134.1, 129.5, 128.5, 127.9, 117.0, 100.4, 44.3, 21.1. IR (cm^{-1}) 3338 (NH), 3073, 3020 (CH), 2217 (CN), 1655 (CO), 1583, 1532 (C=C), 1436 (CH_2), 1360 (CH_3), 808 (*p*-C Ph).

2-Cyano-3-(thiophene-2-yl)-*N*-(4-biphenyl)acrylamide (22g). 2-Cyano-*N*-(4-biphenyl)acetamide (**21d**) was synthesised by stirring methyl cyanoacetate (0.20 g, 2.0 mmol) with 4-phenylbenzylamine (0.37 g, 2.0 mmol) in MeOH at room temperature for 60 min. After this time the solution was filtered and washed with cold MeOH and dried under suction to afford **21d** as a white solid; 67%; mp 164–166 °C. This material was used directly for the synthesis of **22g**.

LRMS (ESI^+) *m/z* 251 (M + 1). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.60–7.56 (m, 5H), 7.46–7.43 (m, 2H), 7.40–7.34 (m, 2H), 6.41 (s, 1H), 4.53 (d, J = 5.7 Hz, 2H), 3.43 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 160.7, 141.1, 140.5, 135.7, 128.9, 128.4, 127.7, 127.5, 127.1, 114.6, 44.1, 25.9. IR (cm^{-1}) 3312 (NH), 3098, 3055, 3034, 2960, 2921 (CH), 2259 (CN), 1656 (CO), 1557 (C=C), 1450 (CH_2), 816 (*p*-C Ph).

Thiophene-2-carboxaldehyde (0.2 g, 1.8 mmol) and 3-fluorophenylacetonitrile (0.45 g, 1.8 mmol) were added together in EtOH (4 mL). Piperidine (cat.) was added and the reaction was irradiated with microwaves (120 °C, 200 W) for 20 min and then placed in the freezer for 60 min. The solution was filtered and washed with cold EtOH and dried under suction to afford **22g** as an orange solid; 57%; mp 183–185 °C.

LRMS (ESI^+) *m/z* 345 (M + 1). ^1H NMR (DMSO-d_6, 400 MHz): δ 8.98 (s, 1H), 8.47 (s, 1H), 8.11 (d, J = 5.0 Hz, 1H), 7.91 (d, J = 3.2 Hz, 1H), 7.64 (dd, J = 7.6, 6.1 Hz, 4H), 7.49–7.40 (m, 4H), 7.39–7.29 (m, 2H), 4.46 (d, J = 5.7 Hz, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 161.5, 144.2, 140.4, 139.4, 138.7, 138.5, 136.3, 135.5, 129.4, 129.1, 128.5, 127.8, 127.1, 127.1, 117.0, 102.0, 43.4. IR (cm^{-1}) 3323 (NH), 3104, 3086, 3025, 2971 (CH), 2221 (CN), 1655 (CO), 1583, 1537 (C=C), 1414 (CH_2), 810 (*p*-C Ph).

General procedure 4 – concurrent olefin and furan reduction

2-Cyano-*N*-(4-methoxybenzyl)-3-(tetrahydrofuran-2-yl)propanamide (28a). (*E*)-2-Cyano-3-(furan-2-yl)-*N*-(4-methoxybenzyl) acrylamide **22a** (0.1 g, 0.35 mmol) was dissolved in sufficient MeOH (7 mL) to form a 0.05 M solution. This solution was hydrogenated using the H-Cube™ with a 10% Pd/C catalyst at 1 mL min^{-1} flow rate, 50 °C and 0 bar H_2 pressure. The MeOH was removed *in vacuo* to afford **28a** as a clear oil; 0.1 g, 97%. GC-MS (r.t.) 13.28 min.

MS (ESI^+) *m/z* 285 (M + 1). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21–7.16 (m, 2H), 6.85–6.83 (m, 2H), 6.77 (br s, 1H), 4.43–4.30 (m, 2H), 4.05–3.86 (m, 1H), 3.83–3.78 (m, 1H), 3.77 (s, 3H), 3.75–3.66 (m, 1H), 3.55–3.53 (m, 1H), 2.24–2.17 (m, 1H), 2.09–1.95 (m, 2H), 1.92–1.81 (m, 2H), 1.55–1.54 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.7, 159.3, 129.4, 129.3, 118.2, 114.2, 75.8, 67.9, 55.4, 43.8, 36.3, 35.9, 31.4, 25.7. IR (cm^{-1}) 3303, 3251 (NH), 3077, 2955, 2930, 2830 (CH), 2253 (CN), 1644 (CO), 1611 (C=C), 1552 (NH bend), 1461, 1436 (CH_2), 1351 (CH_3), 1298 (C–O), 1244 (C–O), 1029 (C–O–C), 826 (*p*-C Ph).

General procedure 5 – selective olefin reduction

2-Cyano-3-(furan-2-yl)-*N*-(4-methoxybenzyl)propanamide (25a). (*E*)-2-Cyano-3-(furan-2-yl)-*N*-(4-methoxybenzyl)acrylamide **22a** (0.1 g, 0.35 mmol) was dissolved in MeOH (7 mL) to form a 0.05 M solution. This solution was hydrogenated using the H-Cube Pro™ with a 10% Pd/C catalyst at 3 mL min^{-1} flow rate, 25 °C and 0 bar 10% H_2 pressure. The MeOH was removed *in vacuo* to afford **25a** as a white solid; 100%; mp 121–123 °C. GC-MS (r.t.) 10.09 min.

LRMS (ESI^+) *m/z* 285 (M + 1). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32 (d, J = 1.1 Hz, 1H), 7.15 (d, J = 8.6 Hz, 2H), 6.88–6.83 (m, 2H), 6.34 (br s, NH), 6.31 (dd, J = 3.1, 1.9 Hz, 1H), 6.22 (d, J = 3.2

Hz 1H), 4.47–4.32 (m, 2H), 3.80 (s, 3H), 3.70 (dd, J = 7.8, 5.6 Hz, 1H), 3.32 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 163.4, 159.5, 149.4, 142.6, 129.4, 129.0, 117.6, 114.4, 110.7, 108.6, 55.5, 44.1, 38.2, 28.8. IR (cm^{-1}) 3305 (NH), 3121, 3020, 2931, 2834 (CH), 2251 (CN), 1642 (CO), 1615 (C=C), 1555 (C=C), 1461 (CH_2), 1434 (CH_2), 1247 (CH_3), 1223 (C–O), 813 (*p*-C Ph).

General procedure 6 – selective nitrile and olefin reduction

3-Amino-2-(furan-2-ylmethyl)-*N*-(4-methoxybenzyl)-propanamide (23a). (*E*)-2-Cyano-3-(furan-2-yl)-*N*-(4-methoxybenzyl)-acrylamide **22a** (0.1 g, 0.35 mmol) was dissolved in sufficient MeOH (7 mL) to form a 0.05 M solution. This solution was hydrogenated using the H-Cube Pro™ with a RaNi catalyst at 1 mL min^{-1} flow rate, 50 °C and 10 bar H_2 pressure. The MeOH was removed *in vacuo* to afford **23a** as a clear oil; 100%. GC-MS (r.t.) 13.19 min.

LRMS (ESI^+) *m*/*z* 289 (M + 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (dd, J = 1.9, 0.8 Hz, 1H), 7.12 (d, J = 8.7 Hz, 2H), 6.82 (dd, J = 8.6, 1.9 Hz, 2H), 6.26 (dd, J = 3.1, 1.9 Hz, 1H), 6.09–5.96 (m, 1H), 4.38 (dd, J = 14.6, 5.9 Hz, 1H), 4.29 (dd, J = 14.6, 5.4 Hz, 1H), 3.78 (s, 3H), 3.02 (dd, J = 15.1, 7.5 Hz, 1H), 2.92 (dd, J = 12.7, 8.3 Hz, 1H), 2.88–2.80 (m, 1H), 2.76 (d, J = 15.0 Hz, 1H), 2.56 (dd, J = 17.4, 9.9 Hz, 1H), 1.46 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.8, 158.9, 153.3, 141.3, 130.6, 129.0, 114.0, 110.3, 106.6, 55.3, 48.4, 43.3, 42.8, 28.6. IR (cm^{-1}) 3285 (NH_2), 3065, 2933, 2836 (CH), 1643 (CO), 1612 (C=C), 1548, 1511 (NH bend), 1463, 1440 (CH_2), 1301 (CH_3), 1243 (C–O), 1175 (C–O), 1030 (C–O–C), 808 (*p*-C Ph).

3-Amino-2-(furan-2-ylmethyl)-*N*-(4-chlorobenzyl)propanamide (23b). 2-Cyano-3-(furan-2-yl)-*N*-(4-chlorobenzyl)acrylamide **22b** was hydrogenated using the H-Cube Pro™ with a RaNi catalyst at 1 mL min^{-1} flow rate, 50 °C and 10 bar H_2 pressure. The MeOH was removed *in vacuo* to afford **23b** as a clear oil; 83%.

LRMS (ESI^+) *m*/*z* 293 (M + 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33–7.27 (m, 2H), 7.24 (d, J = 1.8 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.26 (dd, J = 3.0, 2.0 Hz, 1H), 6.04 (d, J = 2.9 Hz, 1H), 4.45 (dd, J = 9.6, 5.7 Hz, 1H), 4.29 (dd, J = 15.1, 5.4 Hz, 1H), 3.06–3.01 (m, 1H), 2.94 (dt, J = 21.5, 8.4 Hz, 2H), 2.80 (dd, J = 15.0, 7.2 Hz, 1H), 2.67 (dd, J = 7.8, 4.3 Hz, 1H), 2.39 (br s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.9, 152.9, 141.4, 137.0, 129.0, 128.7, 127.6, 110.4, 106.8, 47.5, 42.9, 42.6, 28.6. IR (cm^{-1}) 3330 (NH), 3121, 3014, 2931, 2834 (CH), 16412 (CO), 1615 (C=C), 1552 (C=C), 1462, 1430 (CH_2), 1223 (C–O), 813 (*p*-C Ph), 547 (Cl–C Ph).

3-Amino-2-(furan-2-ylmethyl)-*N*-(4-methylbenzyl)propanamide (23c). 2-Cyno-3-(furan-2-yl)-*N*-(4-methylbenzyl)acrylamide (**22c**) was hydrogenated using the H-Cube Pro™ with a RaNi catalyst at 1 mL min^{-1} flow rate, 50 °C and 10 bar H_2 pressure. The MeOH was removed *in vacuo* to afford **23c** as a clear oil, 85%.

LRMS (ESI^+) *m*/*z* 273 (M + 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28–7.26 (m, 1H), 7.19–7.09 (m, 4H), 6.27 (t, J = 2.2 Hz, 1H), 6.02 (d, J = 3.1 Hz, 1H), 4.43–4.31 (m, 2H), 3.04 (dd, J = 15.1, 7.4 Hz, 1H), 2.92 (dd, J = 12.7, 8.4 Hz, 1H), 2.85 (dd, J = 7.8, 4.8 Hz, 1H), 2.77 (dd, J = 15.1, 7.4 Hz, 1H), 2.56 (qd, J = 7.6, 4.1 Hz, 1H), 2.32 (s, 3H), 1.35 (br s, NH). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.9, 153.3, 141.3, 136.9, 135.4, 129.26, 127.6, 110.3, 106.6, 48.4, 43.3, 43.1, 28.6, 21.1. IR (cm^{-1}) 3305 (NH), 3121, 3020, 2931, 2834 (CH), 2251 (CN), 1642 (CO), 1615 (C=C), 1555 (C=C), 1461 (CH_2), 1434 (CH_2), 1247 (CH_3), 1223 (C–O), 813 (*p*-C Ph) 550 (Cl–C Ph).

3-Amino-2-(pyrrole-2-ylmethyl)-*N*-(4-methoxybenzyl)propanamide (23d). (*E*)-2-Cyano-3-(pyrrole-2-yl)-*N*-(4-methoxybenzyl) acrylamide **31** was hydrogenated using the H-Cube Pro™ with a RaNi catalyst at 1 mL min^{-1} flow rate, 50 °C and 10 bar H_2 pressure. The MeOH was removed *in vacuo* to afford **23d** as a yellow oil; 77%.

LRMS (ESI^+) *m*/*z* 288 (M + 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.05 (s, NH), 7.76 (s, NH), 7.11 (d, J = 8.7 Hz, 2H), 6.86–6.80 (m, 2H), 6.61 (dd, J = 4.1, 2.6 Hz, 1H), 6.07–6.05 (m, 1H), 5.88 (s, 1H), 4.40–4.29 (m, 2H), 3.78 (s, 3H), 2.98–2.83 (m, 3H), 2.82–2.77 (m, 1H), 2.46–2.40 (m, 1H), 1.40 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.2, 158.9, 130.5, 129.5, 128.8, 116.9, 114.0, 107.6, 106.3, 55.3, 48.7, 43.9, 42.81, 27.9. IR (cm^{-1}) 3310 (NH), 3101, 3025, 2899, 2835 (CH), 1642 (CO), 1618 (C=C), 1532 (C=C), 1463 (CH_2), 1434 (CH_2), 1249 (CH_3), 1223 (C–O), 813 (*p*-C Ph).

3-Amino-2-(pyrrole-2-ylmethyl)-*N*-(4-chlorobenzyl)propanamide (23e). (*E*)-2-Cyano-3-(pyrrole-2-yl)-*N*-(4-chlorobenzyl)acrylamide **22d** was hydrogenated using the H-Cube Pro™ with a RaNi catalyst at 1 mL min^{-1} flow rate, 50 °C and 10 bar H_2 pressure. The MeOH was removed *in vacuo* to afford **23e** as a clear oil; 84%.

LRMS (ESI^+) *m*/*z* 292 (M + 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.97 (s, NH), 8.03 (s, NH), 7.26 (t, J = 3.2 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.62 (dd, J = 4.1, 2.6 Hz, 1H), 6.07 (dd, J = 5.6, 2.8 Hz, 1H), 5.89 (s, 1H), 4.38 (qd, J = 15.1, 5.9 Hz, 2H), 3.12–2.64 (m, 4H), 2.47 (td, J = 9.1, 4.5 Hz, 1H), 1.57 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.4, 137.0, 133.0, 128.8, 128.8, 117.0, 107.7, 106.4, 48.4, 43.9, 42.6, 27.9. IR (cm^{-1}) 3287 (NH), 3084, 3035 2923, 2860 (CH), 1644 (CO), 1540, 1514 (C=C), 1434 (CH_2), 808 (*p*-C Ph), 519 (Cl–C Ph).

2-(3-Fluorophenyl)-3-(1*H*-pyrrol-2-yl)propan-1-amine (23f). (*E*)-2-Cyano-3-(furan-2-yl)-*N*-(4-methoxybenzyl)acrylamide **22e** was hydrogenated using the H-Cube Pro™ with a RaNi catalyst at 1 mL min^{-1} flow rate, 50 °C and 10 bar H_2 pressure. The MeOH was removed *in vacuo* to afford **23f** as a yellow oil; 100%.

LRMS (ESI^+) *m*/*z* 219 (M + 1). ^{1}H NMR (Acetone, 400 MHz): δ 8.60 (s, 1H), 7.39–7.22 (m, 1H), 7.05–6.87 (m, 3H), 6.61 (dd, J = 3.9, 2.4 Hz, 1H), 6.10 (dd, J = 5.5, 2.8 Hz, 1H), 5.88 (s, 1H), 3.06–2.82 (m, 5H). ^{13}C NMR (acetone, 101 MHz): δ 164.3, 146.0, 130.2, 129.7, 123.6, 116.6, 114.5, 113.6, 108.1, 106.4, 49.5, 46.9, 32.3. IR (cm^{-1}) 3288 (NH), 3029, 2965 (CH), 1612, 1515 (C=C), 1049 (F–C Ph), 759 (*m*-C Ph).

3-Amino-2-(thiophene-2-ylmethyl)-*N*-(4-methoxybenzyl)propanamide (23g). (*E*)-2-Cyano-3-(thiophene-2-yl)-*N*-(4-methoxybenzyl)acrylamide **32** was hydrogenated using the H-Cube Pro™ with a RaNi catalyst at 1 mL min^{-1} flow rate, 50 °C and 10 bar H_2 pressure. The MeOH was removed *in vacuo* to afford **23g** as a clear oil, 88%.

LRMS (ESI^+) *m*/*z* 305 (M + 1). ^{1}H NMR (acetone, 400 MHz): δ 7.59 (s, 1H), 7.23 (dd, J = 5.1, 1.0 Hz, 2H), 7.13 (d, J = 8.7 Hz, 2H), 6.91 (dd, J = 5.1, 3.4 Hz, 1H), 6.83–6.81 (m, 2H), 4.29 (dd, J = 25.4, 5.9 Hz, 2H), 3.76 (d, J = 1.2 Hz, 3H), 3.74 (d, J = 0.9 Hz, 1H), 3.41 (dd, J = 14.0, 7.9 Hz, 1H), 3.30 (d, J = 7.5 Hz, 1H), 3.21–

3.16 (m, 1H), 3.04 (dd, J = 14.6, 6.2 Hz, 1H), 1.28 (s, 2H). ^{13}C NMR (Acetone, 101 MHz): δ 173.2, 158.7, 142.6, 131.6, 128.6, 128.5, 126.6, 125.4, 123.43, 113.5, 54.6, 53.0, 50.1, 41.9, 30.3. IR (cm^{-1}) 3285 (NH), 3106, 3056, 2834 (CH), 1645 (CO), 1612, 1534 (C=C), 1415 (CH_2), 1319 (CH_3), 1250 (C–O), 1030 (C–O–C), 812 (*p*-C Ph).

3-Amino-2-(thiophene-2-ylmethyl)-*N*-(4-methylbenzyl)propanamide (23h). (*E*)-2-Cyano-3-(thiophene-2-yl)-*N*-(4-methylbenzyl)acrylamide **22f** was hydrogenated using the H-Cube Pro™ with a RaNi catalyst at 1 mL min^{-1} flow rate, 50 °C and 10 bar H_2 pressure. The MeOH was removed *in vacuo* to afford **23h** as a yellow oil; 100%.

LRMS (ESI^+) m/z 289 (M + 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12 (dd, J = 5.1, 1.0 Hz, 1H), 7.08 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 7.9 Hz, 2H), 6.90 (dd, J = 5.1, 3.5 Hz, 1H), 6.79 (d, J = 3.0 Hz, 1H), 4.39–4.31 (m, 2H), 3.28–3.13 (m, 1H), 3.04–2.88 (m, 2H), 2.53–2.42 (m, 1H), 2.31 (s, 3H), 2.28 (dd, J = 11.7, 5.2 Hz, 1H), 1.38–1.17 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.7, 141.9, 135.3, 129.3, 127.6, 126.9, 125.8, 123.8, 114.1, 51.7, 43.3, 43.2, 30.3, 21.1. IR (cm^{-1}) 3238 (NH), 3054, 3020 (CH), 1650 (CO), 1580, 1512 (C=C), 1426 (CH_2), 1360 (CH_3), 808 (*p*-C Ph).

3-Amino-2-(thiophene-2-ylmethyl)-*N*-(4-biphenyl)propanamide (23i). (*E*)-2-Cyano-3-(furan-2-yl)-*N*-(4-methoxybenzyl)acrylamide **22i** was hydrogenated using the H-Cube Pro™ with a RaNi catalyst at 1 mL min^{-1} flow rate, 50 °C and 10 bar H_2 pressure. The MeOH was removed *in vacuo* to afford **23g** as a clear oil; 83%.

LRMS (ESI^+) m/z 340 (M + 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56–7.48 (m, 3H), 7.45–7.32 (m, 5H), 7.21 (d, J = 8.1 Hz, 1H), 7.13 (dd, J = 3.8, 1.3 Hz, 1H), 6.98–6.86 (m, 1H), 6.82 (d, J = 3.0 Hz, 1H), 4.51–4.38 (m, 2H), 3.26 (dd, J = 9.3, 5.2 Hz, 1H), 3.02–2.91 (m, 2H), 2.83 (d, J = 12.0 Hz, 1H), 2.51 (dd, J = 7.4, 4.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.8, 140.8, 140.3, 137.8, 137.4, 128.8, 128.1, 128.0, 127.4, 127.1, 123.8, 31.9, 30.2, 22.5, 14.0. IR (cm^{-1}) 3287 (NH), 3060, 2930, 2858 (CH), 1643 (CO), 1612, 1511 (C=C), 1462 (CH_2), 1440 (CH_2), 818 (*p*-C Ph).

General procedure 7 – reaction path B

3-(2-(Furan-2-ylmethyl)-3-(4-methoxybenzylamino)-3-oxopropylcarbamoyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (24a). 3-Amino-2-(furan-2-ylmethyl)-*N*-(4-methoxybenzyl)propanamide (**23a**) (0.35 g, 1.2 mmol) and norcantharidin (**2**) (0.20 g, 1.8 mmol) were dissolved separately in acetone (10 mL × 2) and the solutions were added together and the reaction was left to stir at room temperature for 4 hours. The solution was filtered and washed with cold acetone and dried under suction to afford **24a** as a white solid; 0.30 g, 55%; mp 168–170 °C.

MS (ESI^-) m/z 455 (M − 1). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.91 (br s, OH), 8.21 (t, J = 5.4 Hz, NH), 7.49 (d, J = 1.0 Hz, NH), 7.40 (t, J = 5.9 Hz, NH), 7.07 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.34 (dd, J = 3.0, 1.9 Hz, 1H), 6.08 (d, J = 2.9 Hz, 1H), 4.73 (d, J = 3.7 Hz, 1H), 4.40 (d, J = 3.8 Hz, 1H), 4.22 (dd, J = 14.9, 6.0 Hz, 1H), 4.11 (dd, J = 14.9, 5.6 Hz, 1H), 3.72 (s, 3H), 3.24–3.18 (m, 1H), 3.07–2.99 (m, 1H), 2.83 (s, 2H), 2.77–2.68 (m, 3H), 1.57–1.40 (m, 4H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 173.0, 172.7, 171.3, 158.6, 153.7, 141.9, 131.7, 128.9, 114.0, 110.8, 106.6, 79.3, 77.2, 55.5, 53.6, 52.0, 45.2, 42.0, 41.3, 29.2, 28.8, 28.6. IR (cm^{-1}) 3295 (NH), 3091 (OH), 2985, 2937 (CH), 1692 (CO), 1651 (C=C), 1562, 1514 (NH bend), 1302 (CH_3), 1247 (C–O), 1032 (CH_3), 818 (*p*-C Ph), 731 (CH_2 bend).

3-(2-(Furan-2-ylmethyl)-3-(4-chlorobenzylamino)-3-oxopropylcarbamoyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (24b). Synthesised as described in general procedure 7 – sequential reaction Path B to afford **16b** as a white solid (diastereomers collected in a 1 : 1 ratio); 0.3 g, overall yield 56%; mp 166 °C.

MS (ESI^-) m/z 459 (M − 1). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.91 (br s, OH), 8.45 (t, J = 6.0 Hz, NH), 7.66 (t, J = 5.8 Hz, NH), 7.50 (d, J = 1.1 Hz, 1H), 7.32 (dd, J = 8.3, 1.5 Hz, 1H), 7.16 (t, J = 8.6 Hz, 2H), 6.35 (t, J = 11.7, 2.9 Hz, 1H), 6.09 (dd, J = 11.7, 2.9 Hz, 1H), 4.72 (dd, J = 3.5, 2.4 Hz, 1H), 4.40 (d, J = 3.4 Hz, 1H), 4.30–4.14 (m, 2H), 3.27–3.18 (m, 2H), 3.06–3.01 (m, 1H), 2.85–2.67 (m, 5H), 1.56–1.47 (m, 4H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 173.1, 173.0*, 171.3, 171.2*, 153.6, 153.6*, 142.0, 139.0, 138.9*, 131.6, 129.5, 129.4*, 128.5, 127.6, 110.8, 106.7, 106.6*, 79.3, 79.2*, 77.2, 77.2*, 53.6, 53.3*, 51.9, 51.6*, 45.3, 45.0*, 41.8, 41.3*, 29.4, 29.2*, 28.9, 28.8, 28.6*. IR (cm^{-1}) 3309 (NH), 3063 (OH), 2984, 2967, 2920, 2879 (CH), 1729 (CO), 1692 (CO), 1647 (C=C), 1537 (NH bend), 1247 (C–O), 1183 (C–O), 819 (*p*-C Ph), 737 (CH_2 bend), 696 (C–Cl). *Diastereomers peaks.

3-(2-(Furan-2-ylmethyl)-3-(4-methylbenzylamino)-3-oxopropylcarbamoyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (24c). Synthesised as described in general procedure 7 – sequential reaction path B to afford **24c** as a white solid (diastereomers collected in a 1 : 1 ratio); 0.42 g, overall yield 60%; mp 166–167 °C.

MS (ESI^-) m/z 439 (M − 1). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.92 (br s, OH), 8.37 (t, J = 5.6 Hz, NH), 8.22 (t, J = 5.5 Hz, NH)*, 7.62 (t, J = 5.6 Hz, NH), 7.42 (t, J = 5.4 Hz, NH)*, 7.12–7.01 (m, 4H), 6.34 (s, 1H), 6.10 (dd, J = 12.0, 2.7 Hz, 1H), 4.72 (d, J = 10.0 Hz, 1H), 4.41 (s, 1H), 4.27–4.13 (m, 2H), 3.25–3.21 (m, 2H), 3.06–3.03 (m, 2H), 2.85–2.68 (m, 5H), 2.26 (s, 3H), 1.56–1.40 (m, 4H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 173.0, 172.9*, 172.9, 172.8*, 171.3, 171.2*, 153.7, 153.7*, 141.9, 141.9*, 136.8, 136.7*, 136.1, 136.0*, 129.2, 127.6*, 110.8, 106.5, 106.6*, 79.3, 79.2*, 77.2, 77.2*, 53.6, 53.3*, 52.0, 51.7*, 45.2, 45.0*, 42.3, 41.3, 31.2, 29.4, 29.2*, 28.9, 28.8*, 28.8, 28.6*, 21.1. IR (cm^{-1}) 3306 (NH), 3001 (OH), 2984, 2947, 2919, 2871 (CH), 1729 (CO), 1692 (CO), 1644 (C=C), 1537 (NH bend), 1381 (CH_3), 1251 (C–O), 1180 (C–O), 835 (*p*-Ar), 738 (CH_2 bend). *Diastereomers peaks.

General procedure 8 – reaction path B, with selective nitrile and olefin reduction of thiophene and pyrrole based analogues

3-(2-(Pyrrole-2-ylmethyl)-3-(4-methoxybenzylamino)-3-oxopropylcarbamoyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (24d). 3-Amino-2-(pyrrole-2-ylmethyl)-*N*-(4-methoxybenzyl) propanamide **22d** (0.14 g, 0.50 mmol) was dissolved in sufficient EtOH : EtoAc (1 : 1) (10 mL) to form a 0.05 M solution. This solution was hydrogenated using the H-Cube Pro™ with a RaNi catalyst at 1 mL min^{-1} flow rate, 70 °C and 70 bar H_2 pressure. The solvent was removed *in vacuo* and to afford 2-((1*H*-pyrrol-2-yl)methyl)-3-amino-*N*-(4-methoxybenzyl)propanamide as a yellow oil, 0.11 g, 77%. The crude product and norcantharidin

(**2**) (0.20 g, 1.8 mmol) were dissolved separately in acetone (10 mL × 2) and the solutions were added together and the reaction was left to stir at room temperature for 4 hours. The solution was filtered and washed with cold acetone and dried under suction to afford **24d** as a white solid; 0.18 g, overall yield 26%; mp 166 °C.

MS (ESI^-) *m*/*z* 517 (M − 1). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.89 (br s, OH), 10.39 (s, NH), 8.20 (t, J = 5.5 Hz, NH), 8.07 (t, J = 5.3 Hz, NH)*, 7.50 (t, J = 5.4 Hz, NH), 7.29 (t, J = 5.3 Hz, NH)*, 7.07 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.55 (s, 2H), 5.90–5.75 (m, 2H), 4.71 (s, 1H), 4.39 (s, 1H), 4.23–4.13 (m, 2H), 3.71 (s, 3H), 3.21–3.15 (m, 1H), 3.07 (dd, J = 12.0, 5.7 Hz, 1H), 2.86–2.61 (m, 5H), 1.55–1.39 (m, 4H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 174.0, 173.0, 172.8, 171.2, 142.1, 142.02, 140.5, 139.4, 139.1, 139.0, 129.4, 128.4, 128.3, 128.2, 127.8, 127.2, 127.0, 126.9, 126.0, 124.5, 79.3, 79.2, 77.2, 53.7, 53.3, 51.8, 48.4, 48.1, 42.2, 41.4, 31.7, 30.4, 29.4, 29.2, 28.9, 26.8, 22.5, 14.3. IR (cm^{-1}) 3432 (NH), 3306 (NH), 3074 (OH), 2992, 2937, 2882, 2834 (CH), 1685 (CO), 1653 (CO), 1635 (C═C), 1538, 1513 (NH bend), 1302 (CH_3), 1245, 1223 (C–O), 806 (*p*-C Ph). *Diasteromer peaks.

3-(2-(Pyrrole-2-ylmethyl)-3-(4-chlorobenzylamino)-3-oxopropylcarbamoyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (24e). Synthesised as described in general procedure 8 – sequential reaction Path B to afford **24e** as a pale brown solid (diastereomers collected in a 1 : 0.7 ratio); 0.1 g, overall yield 27%; mp 129–131 °C.

MS (ESI^-) *m*/*z* 459 (M − 1). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.94 (br s, OH), 8.45 (t, J = 6.1 Hz, NH), 8.30 (t, J = 5.8 Hz, NH), 7.67 (t, J = 5.6 Hz, NH), 7.43 (t, J = 5.7 Hz, NH), 7.32 (d, J = 8.3 Hz, 2H), 7.17 (t, J = 8.5 Hz, 2H), 6.14 (d, J = 2.9 Hz, 1H), 6.01 (dd, J = 12.6, 2.9 Hz, 1H), 5.11 (t, J = 5.5 Hz, 1H), 4.74 (d, J = 3.1 Hz, 1H), 4.71 (s, 1H), 4.41 (d, J = 12.9 Hz, 1H), 4.31 (d, J = 5.2 Hz, 2H), 4.29–4.14 (m, 2H), 3.26–3.20 (m, 1H), 3.06 (d, J = 5.4 Hz, 1H), 2.87–2.67 (m, 5H), 1.57–1.41 (m, 4H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 173.5, 173.1*, 173.0, 172.9*, 171.3, 171.2*, 154.4, 152.9, 152.8*, 139.0, 138.9*, 131.6, 129.5, 129.4*, 128.6, 128.5*, 127.6, 108.0, 107.1*, 80.1, 79.3, 79.2*, 77.2, 56.1, 53.6, 53.2*, 51.9, 51.6*, 51.2, 45.1, 44.9*, 41.9, 41.3*, 31.2, 29.2*, 28.9, 28.8*, 28.8, 27.9*. IR (cm^{-1}) 3292 (NH), 3087 (OH), 2987, 2984, 2920, 2875 (CH), 1702 (CO), 1646 (C═C), 1545, 1494 (NH bend), 1240, 1200 (C–O), 1170 (C–O), 799 (*p*-C Ph). *Diastereomers peaks.

3-(2-(pyrrole-2-ylmethyl)-3-(3-fluorophenyl))-7-oxabicyclo-[2.2.1]heptane-2-carboxylic acid (24f). Synthesised as described in general procedure 8 – sequential reaction Path B to afford **24f** as a yellow oil, 0.08 g, overall yield 15%.

MS (ESI^-) *m*/*z* 385 (M − 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (br s, NH), 7.27–7.24 (m, 1H), 6.94 (td, J = 8.1, 2.2 Hz, 2H), 6.90–6.85 (m, 1H), 6.63 (dd, J = 4.0, 2.8 Hz, 1H), 6.06 (dd, J = 6.0, 2.8 Hz, 1H), 5.77 (s, 1H), 4.83 (dt, J = 5.2, 2.8 Hz, 2H), 3.77 (dd, J = 13.4, 8.4 Hz, 1H), 3.66 (dd, J = 13.4, 6.4 Hz, 1H), 3.42–3.33 (m, 1H), 2.91 (d, J = 6.9 Hz, 2H), 2.76 (d, J = 7.3 Hz, 2H), 1.90–1.83 (m, 2H), 1.60 (q, J = 6.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 177.4, 177.4, 162.8 (d, J = 246 Hz), 143.9, 130.0, 128.8, 123.5, 116.7, 114.7, 114.1, 108.3, 106.9, 79.1, 77.2, 49.8, 49.8, 43.6, 31.4, 28.6, 28.5.

3-(2-(Thiophene-2-ylmethyl)-3-(4-methoxybenzylamino)-3-oxopropylcarbamoyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (24g). Synthesised as described in general procedure 8 – sequential reaction Path B to afford **24g** as a white solid; 0.1 g, overall yield 41%; mp 158–159 °C.

MS (ESI^-) *m*/*z* 471 (M − 1).[1] H NMR (DMSO-d_6, 400 MHz): δ 11.89 (br s, 1H), 8.33 (t, J = 4.7 Hz, NH), 8.20 (t, J = 5.6 Hz, NH)*, 7.58 (t, J = 5.9 Hz, NH), 7.40 (t, J = 6.2 Hz, NH)*, 7.30 (d, J = 5.2 Hz, 1H), 7.25 (t, J = 6.0 Hz, 1H)*, 7.17 (d, J = 8.5 Hz, 2H), 7.03 (t, J = 8.2 Hz, 2H), 6.98–6.87 (m, 1H), 6.90–6.74 (m, 3H), 4.72 (d, J = 9.9 Hz, 1H), 4.41 (d, J = 2.8 Hz, 1H)*, 4.37 (d, J = 4.0 Hz, 1H)*, 4.23–4.09 (m, 2H), 3.71 (s, 3H), 3.26–3.17 (m, 1H), 3.05 (dd, J = 12.8, 7.5 Hz, 1H), 3.01–2.93 (m, 1H), 2.93–2.66 (m, 4H), 1.55–1.38 (m, 4H). ^{13}C NMR (DMSO-d_6, 101 MHz): 172.9, 172.8, 171.2, 158.5, 142.1, 142.0*, 131.8, 129.0*, 128.9, 127.2, 126.0, 124.4, 114.0, 79.2, 77.3, 55.5, 53.4, 48.0, 42.0, 41.3, 30.4, 29.4, 28.9, 22.5. IR (cm^{-1}) 3308 (NH), 3078 (OH), 2984, 2964, 2921, 2874 (CH), 1694 (CO), 1646 (C═C), 1545, (NH bend), 1382 (CH_3), 1242 (C–O), 817 (*p*-C Ph). * Diastereomers peaks.

3-(2-(Thiophene-2-ylmethyl)-3-(4-methylbenzylamino)-3-oxopropylcarbamoyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (24h). Synthesised as described in general procedure 8 – sequential reaction Path B to afford **24h** as a white solid (diastereomers collected in a 1 : 1 ratio); 0.13 g, overall yield 38%; mp 161–163 °C.

MS (ESI^-) *m*/*z* 455 (M − 1). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.91 (br s, OH), 8.33 (t, J = 5.8 Hz, NH)*, 8.2 (t, J = 5.8 Hz, NH), 7.61 (t, J = 5.7 Hz, NH)*, 7.41 (t, J = 5.8 Hz, NH), 7.32 (dd, J = 5.1, 0.8 Hz, 1H), 7.05 (d, J = 7.9 Hz, 2H), 6.98 (t, J = 8.5 Hz, 2H), 6.94–6.90 (m, 1H), 6.83 (dd, J = 8.9, 2.9 Hz, 1H), 4.75–4.69 (m, 1H)*, 4.42 (d, J = 3.3 Hz, 1H), 4.27–4.11 (m, 2H), 3.27–3.19 (m, 1H), 3.09–2.95 (m, 2H), 2.89 (dd, J = 12.3, 6.9 Hz, 1H), 2.84–2.67 (m, 2H), 2.51–2.49 (m, 2H), 2.25 (s, 3H), 1.57–1.40 (m, 4H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 172.9, 172.8*, 172.7, 171.2*, 171.1, 142.1, 142.0*, 136.8, 136.6*, 136.1, 136.0*, 129.1, 127.6, 127.2*, 126.0, 124.4, 80.1, 79.3, 79.2*, 77.2, 77.2*, 53.6, 53.3*, 51.9, 51.7*, 51.2, 48.3, 48.0*, 42.3, 41.3*, 30.4, 30.2*, 29.4, 29.2*, 28.9, 28.8*, 21.1. IR (cm^{-1}) 3310 (NH), 3062 (OH), 2986, 2963, 2920, 2874 (CH), 1695 (CO), 1646 (C═C), 1545, (NH bend), 1382 (CH_3), 1244 (C–O), 816 (*p*-C Ph). *Diastereomers peaks.

3-(2-(Thiophene-2-ylmethyl)-3-(4-biphenylamino)-3-oxopropylcarbamoyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (24i). Synthesised as described in general procedure 8 – sequential reaction Path B to afford **24i** as a white solid (diastereomers collected in a 1 : 1 ratio); 0.23 g, overall yield 46%; mp 171–174 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.89 (br s, OH), 8.44 (t, J = 5.3 Hz, NH), 8.31 (t, J = 5.6 Hz, NH)*, 7.63 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 2.1 Hz, 1H)*, 7.59 (d, J = 2.3 Hz, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H), 7.35 (dd, J = 8.8, 6.2 Hz, 2H), 7.18 (t, J = 8.6 Hz, 2H), 6.97–6.91 (m, 1H), 6.85 (dd, J = 8.7, 3.2 Hz, 1H), 4.73 (d, J = 11.1 Hz, 1H), 4.50–4.40 (m, 1H), 4.37–4.09 (m, 2H). 3.25 (d, J = 7.0 Hz, 1H), 3.08 (dd, J = 8.0, 5.2 Hz, 1H), 2.96–2.71 (m, 5H), 1.46–1.37 (m, 2H), 1.27–1.17 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 174.0, 173.0, 172.8, 171.2, 142.1, 142.02, 140.5, 139.4, 139.1, 139.0, 129.4, 128.4, 128.3, 128.2, 127.8, 127.2, 127.0, 126.9, 126.0, 124.5, 79.3, 79.2, 77.2, 53.7, 53.3, 51.8, 48.4, 48.1, 42.2, 41.4, 31.7, 30.4, 29.4, 29.2, 28.9, 26.8, 22.5, 14.3. IR (cm^{-1}) 3316 (NH), 3070 (OH), 3033, 2985, 2923, 2876 (CH), 1691 (CO), 1646 (C═C), 1534, 1487 (NH bend), 1242, (C–O), 819 (*p*-C Ph). *Diastereomers peaks.

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